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(54) **BISPECIFIC ANTAGONIST COMPRISING A
LAG-3 BINDING DOMAIN**

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(57) **ABSTRACT**

Antitumor antagonists that bind specifically to immune
checkpoint regulator are disclosed. Also disclosed is a
method of treating proliferative disorders with the antitumor
antagonists.

19 Claims, 50 Drawing Sheets

Specification includes a Sequence Listing.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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Anti-TIGIT mab sequences

Mab	Heavy Chain CDR1	Heavy Chain CDR2	Heavy Chain CDR3
T-01	SDYAWN (SEQ ID:1)	YISYSGSTGYNPSLKS	RMIGVAMDY (SEQ ID:3)
T-02	SDYAWN (1)	YITYSGGTSYNPSLKS	RQIGLGFTY (SEQ ID:5)
T-03	DHTIH (SEQ ID:6)	YFYPRDGSTKYNEKFKG	GMLRWFAD (SEQ ID:8)
T-04	DHTIH (6)	YIYPRDGS SKYNV KFKG	GMLRWFAY (SEQ ID:10)
T-05	DQAIH (SEQ ID:11)	YIYPRDGS TKYNE TFKG	GMLRWFAY (10)
T-06	SDYAWN (1)	YITYSGSTSYNPSLKS	RQVGLGFAY (SEQ ID:14)
T-07	SDSAWN (SEQ ID:15)	YITYSGSTNYNPSLRS	RQVGLGFAY (14)
T-08	NYGMN (SEQ ID:17)	WINTYTGEPTYADDFKG	APPYGYDVRFAY (SEQ ID:19)
T-09	TFAMGVG (SEQ ID:20)	HIWWDDDDKYYPNPA LKS	MDYSYFAWFAY (SEQ ID:22)
T-10 (B21-35)	SYMH (SEQ ID:23)	INPSGGRTSYAQM FQG	DREEQWPVGGFDY (SEQ ID:25)
Mab	Light Chain CDR1	Light Chain CDR2	Light Chain CDR3
T-01	KASQDVS TVVA (SEQ ID:26)	SASYRYT (SEQ ID:27)	QQHYSTPWT (SEQ ID:28)
T-02	KASQDLSTAVA (SEQ ID:29)	SSSYRYT (SEQ ID:30)	QQHYSTPWT (28)
T-03	KASQDVS TTVA (SEQ ID:31)	SASYRYT (27)	QQHYSTPLT (SEQ ID:32)
T-04	KASQDVFTAVA (SEQ ID:33)	SASYRYT (27)	QQHYSIPLT (SEQ ID:34)
T-05	KASQDVS TAVA (SEQ ID:35)	SASYRYT (27)	QQHYSTPLT (32)
T-06	KASQDVS TAVA (35)	SASYHYT (SEQ ID:36)	QQHYSTPWT (28)
T-07	KASQDVS TAVA (35)	SASYRFT (SEQ ID:37)	QHHYSTPWT (SEQ ID:38)
T-08	RSSQSIVHSNGNTYLE (SEQ ID:39)	KVSDRFS (SEQ ID:40)	FQGSHPVWT (SEQ ID:41)
T-09	RSSTGAVTTSNYAN (SEQ ID:42)	GTNNRAP (SEQ ID:43)	ALWYSNHWV (SEQ ID:44)
T-10	RASQSIRRYLN (SEQ ID:45)	SASNLS (SEQ ID:46)	QQSYIIPPT (SEQ ID:47)

FIG. 1

Anti-TIGIT Antibody Variable Domain Sequences

T-01

VH (SEQ ID NO: 48)

QVQLQESGPGGLVKPSQTLSTCTVSGYSITSDYAWNWIQQPGKGLEWIGYISYSGSTGY
NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARRMIGYAMDYWGQGTSVTVSS

VL (SEQ ID NO: 49)

DIQMTQSPSSLSASVGDRVTITCKASQDVSTVVAWHQQKPGKAPKLLIYSASYRYTGVP
SRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPQQHYSTPWTFGGGTKLEIKR

T-02

VH (SEQ ID NO: 50)

QVKLQESGPGGLVKPSQTLSTCTVTGYSITSDYAWNWIQQPGKGLEWIGYITYSGGTSY
NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYSCARRQIGLGFTYWGQGTLLTVSA

VL (SEQ ID NO: 51)

DIQMTQSPSSLSASVGDRVTIPCKASQDLSTAVAWYQQKPGKAPKLLIYSSSYRYTGVP
RFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPQQHYSTPWTFGEGTKLEIK

T-03

VH (SEQ ID NO: 52)

EVQLVQSGAEVKKPGATVKISCKVSGYTFTDHTIHWVQQAPGKGLEWMGYFYPRDGST
KYNEKFKGRVTITADTSTDATAYMELSSLRSEDTAVYYCATGMLRWFADWGQGTLLTVS
VA

VH (SEQ ID NO: 53)

DIQMTQSPSSLSASVGDRVTITCKASQDVSTTVAWYQQKPGKAPKLLIYSASYRYTGVP
SRFSGSGSGTDFTLTISLQPEDFATYYCQQHYSTPLTFGAGTKLELK

FIG. 2A

T-04

VH (SEQ ID NO: 54):

EVQLVQSGAEVKKPGATVKISCKVSGYTFTDHTIHWVQQAPGKGLEWMGYIYPRDGSS
KYNVKFKGRVTITADTSTDATAYMELSSLRSEDVAVYYCATGMLRWFAYWGQGTLVTV
SS

VL (SEQ ID NO: 55):

DIQMTQSPSSLSASVGDRVTITCKASQDVFTAVAWYQQKPGKAPKLLIYSASYRYTGVP
SRFSGSGSGTDFTFTISSLQPEDATYYCQQHYSLPLTFGAGTKLEIK

T-05

VH (SEQ ID NO: 56):

EVQLKQSGAEVKKPGATVKISCKVSGYTFTDQAIHWVQQAPGKGLEWMGYIYPRDGST
KYNETFKGRVTITADTSTDATAYMELSSLRSEDVAVYFCARGMLRWFAYWGQGTLVTVS
S

VL (SEQ ID NO: 57):

DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPLTFGAGTKLELK

T-06

VH (SEQ ID NO: 58):

QVQLQESGPGLVKPSQTLSTCTVSGGSVSSDYAWNWRQPPGKGLEWIGYITYSGSTS
YNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRQVGLGFAYWGQGTLVTVS
A

VL (SEQ ID NO: 59):

DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYHYTGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGKLEIK

T-07

VH (SEQ ID NO: 60):

EVQLQESGPGLVKPSDTLSLTCAVSGYSITSDSAWNWRQPPGKGLEWIGYITYSGSTNY
NPSLRSRVTMSVDTSKNQFSLKLSSVTAVDVAVYYCTRRQVGLGFAYWGQGTLVTVSA

VL (SEQ ID NO: 61):

DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRFTGAP
SRFSGSGSGTDFTLTISSLQPEDFGIYYCQHHYSTPWTFGGGKLEFK

FIG. 2B

T-08

VH (SEQ ID NO: 62):

QVQLVQSGSELKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTG
EPTYADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARAPPYGYDVRFAFWGQG
TLVTVSS

VL (SEQ ID NO: 63):

DVVMTQSPSLPVTLGQPASISCRSSQSIVHSNGNTYLEWFQQRPGQSPRVLIYKVSDRF
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPWTFGRGTKLEIK

T-09

VH (SEQ ID NO: 64):

QVTLKESGPTLVKPTQTLTLCTFSGFSLSTFAMGVGWIRQPPGKALEWLAHIWWDDD
KYYNPALKSRLTITKDTSKNQVVLMTNMDPVDATYYCARMDYSYFAFWGQG
TLVTVSS

VL (SEQ ID NO: 65):

QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQLFRGLIGGTNNRAP
WVPARFSGSLIGDKAALTLSGVQPEDEAEYFCALWYSNHWVFGGGTKLTVL

T-10 (B21-35)

VH (SEQ ID NO: 66):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWWVRQAPGQGLEWMGIINPSGGR
TSYAQMFQGRVTMTRDTSTSTVYMELSSLRSEDVAVYYCARDREEQWPVGGFDYWGG
GTLVTVSS

VL (SEQ ID NO: 67):

DIQMTQSPSSLSASVGDRVTITCRASQSIRRYLNWYQQKPGKAPKLLIYSASNLSGVPS
RFGSGSGTDFTLTISLQPEDFATYYCQQSYIIPPTFGQGTKVEIK

FIG. 2C

Anti-PD1 mab sequences

Mab	Heavy Chain CDR1	Heavy Chain CDR2	Heavy Chain CDR3
PD-01	NFLMS (SEQ ID:68)	TISGGGRDITYYVDSVKG	RTTYSMDY (SEQ ID:70)
PD-02	NSLYY (SEQ ID:71)	GINPSNGGTINFNEKFKT	RDYNYDGGFDS (SEQ ID:73)
PD-03	NSYIY (SEQ ID:74)	GINPSNGGTINFNEKFKT	RRDYRYDGGFDS (SEQ ID:75)
PD-04	NSYIY (74)	GINPSNGGTINFNEKFKT	RDYNYDGGFDS (53)
PD-05 (2P16)	TYYIY (SEQ ID:76)	GINPGNGGTINFNEKFKI	RYHGYDGGCLDY (SEQ ID:78)
PD-06 (2P17)	SVYIH (SEQ ID:79)	WIFPGSGNSKYNENFKG	SETYDYGDY (SEQ ID:81)
Mab	Light Chain CDR1	Light Chain CDR2	Light Chain CDR3
PD-01	LASQTIGTWLA (SEQ ID:82)	AATSLAD (SEQ ID:83)	QQFYSIPWT (SEQ ID:84)
PD-02	RASSILYSNVLH (SEQ ID:85)	RASFLAS (SEQ ID:86)	QQGSSIPLT (SEQ ID:87)
PD-03	SASSSLYSNVLH (SEQ ID:88)	RASFLAS (86)	QQGSSIPLT (87)
PD-04	RASSSLYSNVLH (SEQ ID:89)	RASFLAS (86)	QQGSSIPLT (87)
PD-05	RASKSVSTSGFSVIH (SEQ ID:90)	LASNLES (SEQ ID:91)	QHTWELPNT (SEQ ID:92)
PD-06	KASQNVGTNVA (SEQ ID:93)	SASYRYS (SEQ ID:94)	QQYYSYPYT (SEQ ID:95)

FIG. 3

anti-PD-1 Antibody Variable Domain Sequences

PD-01

VH (SEQ ID NO: 96):

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFLMSWVRQAPGKGLEWVSTISGGGR
DTYYVDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKRTTYSMDYWGQGT
SVTVSS

VL (SEQ ID NO: 97):

DIQMTQSPSSVSASVGDRVITITCLASQTIGTWLAWYQQKPGKAPKLLIYAATSLADG
VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQFY SIPWTFGGGTKLEIK

PD-02

VH (SEQ ID NO: 98):

QVQLVQSGAEVKKPGASVKVSCKASDYTFTNSYLYWLRQAPGQGLEWMGGINPSN
GGTNFNEKFKTRTTSTRDTSISTAYMELSR LRSDDTVVYYCTRRDYN YDGGFDSWG
QGTLVTVSS

VL (SEQ ID NO: 99):

DIQMTQSPSSLSASVGDRVTF TCRASSTLYSNYLHWYQQKPGKAPKLLIYRASFLAS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGSSIPLTFGGGTKVEIK

PD-03

VH (SEQ ID NO: 100)

QVQLVQSGAEVKKPGASVKVSCKASDYTFTNSYIYWVRQAPGQGLEWMGGINPSN
GGTNFNEKFKTRVTSTRDTSISTAYMELSR LRSDDTVVYYCARRDYRYDGGFDSWG
QGTTLTVSS

VL (SEQ ID NO: 101)

DIQMTQSPSSLSASVGDRVITITCSASSSLYSSYLHWYQQKPGKAPKLLIYRASFLASG
VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGSSIPLTFGAGTKLDLK

FIG. 4A

PD-04

VH (SEQ ID NO: 102):

QVQLVQSGAEVKKPGASVKVSCKASDYTFTNSYIYWVRQAPGQGLEWMGGINPSN
GGTNFNEKFKTRVTSTRDTSISTAYMELSRLSDDTVVYYCARRDYN YDGGFDSWG
QGTLVTVSS

VL (SEQ ID NO: 103):

DIQMTQSPSSLSASVGDRVTFTCRASSSLYSNYLHWYQQKPGKAPKLLIYRASFLAS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGSSIPLTFGGGTKVEIK

PD-05

VH (SEQ ID NO: 104):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYIYWVRQAPGQGLEWMGGINPGN
GGTNFNEKFKIRVTMTRDTSISTAYMELSSLRSED TAVYYCARRYHGYDGGGLDYWG
QGTLVTVSS

VL (SEQ ID NO: 105):

DIVLTQSPASLAVSPGQRATITCRASKSVSTSGFSYIHWYQQKPGQPPKLLIYLASNLE
SGVPARFSGSGSGTDFTLTINPVEANDTANYYCQHTWELPNTFGGGGTKVEIK

PD-06

VH (SEQ ID NO: 106):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWMGWIFPGS
GNSKYNENFKGRVTLTADTSTSTVYMELSSLRSED TAVYYCASETYDYGDYWGQGT
LTVSS

VL (SEQ ID NO: 107):

DIQMTQSPSFLSASVGDRVTITCKASQNVGTNVAWYQQKPGKAPKALIYSASYRYS
GVPSRFSGSGSGTEFTLTISLQPEDFATYYCQQYYSPYTFGQGTKLEIK

FIG. 4B

Anti-PD-L1 mab sequences

Mab	Heavy Chain CDR1	Heavy Chain CDR2	Heavy Chain CDR3
PL-01	NYWMH (SEQ ID:108)	MIHPNTNNYNYNEKFKS	SDYGSSPYVFDY (SEQ ID:110)
PL-02	SYWMH (SEQ ID:111)	MIHPNVGSTNYNEKFKS	SRYGSSPYVFDY (SEQ ID:113)
PL-03	SYWMH (111)	MIHPNSGGNNYNEKFKS	SWYGSSPYVFDY (SEQ ID:115)
PL-04	SYWMH (111)	MIHPTGVSTDYNEKFKS	SDYGSSPYVFDY (110)
PL-05	SDYAWN (SEQ ID:117)	YISDSGSTSYNPSLKS	SFLRLRSVFDH (SEQ ID:119)
PL-06	SYGIN (SEQ ID:120)	CYIGNDYTNNEKFKG	AYYGSRV DY (SEQ ID:122)
PL-07	SYGIN (120)	CYIGNDYTNNEKFKG	AYYGSRV DY (122)
PL-08	SYWMH (111)	MIHPNSGGNNYNEKFKS	SWYGSSPYVFDY (115)
Mab	Light Chain CDR1	Light Chain CDR2	Light Chain CDR3
PL-01	RASQDIDNYLN	YTSRLHS (SEQ ID:124)	QQGYTLFWT (SEQ ID:125)
PL-02	RASQDISNYLN	YTSRLQS (SEQ ID:127)	QQGNTLFWT (SEQ ID:128)
PL-03	RASQDISNYLN	YTSRLHS (124)	QQGNTLFWT (128)
PL-04	RASQDISNYLN	YTSRLHS (124)	QQGDTLFWT (SEQ ID:129)
PL-05	KASQDVNVAVA	WASTRHI (SEQ ID:131)	QQHYSTPYT (SEQ ID:132)
PL-06	KASQDINKVIA	YTSTLQP (SEQ ID:134)	LQYDNLYT (SEQ ID:135)
PL-07	QSISDYLN	CASQSISG (SEQ ID:137)	QNGHSFPYT (SEQ ID:138)
PL-08	RASQDIDNYLN	YTSRLHS (124)	QQGYTLFWT (125)

FIG. 5

anti-PD-L1 Antibody Variable Domain Sequences

PL-01

VH (SEQ ID NO: 139):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWMKQAPGQGLEWMGMIHP
NTNNYNYNEKFKSRVTSTRDTSISTAYMELSRRLRSDDTVVYYCARSDYGSSPYYFDY
WGQGTLVTVSS

VL (SEQ ID NO: 140):

DIQMTQSPSSLSASVGDRVTISCRASQDIDNYLNWYQQKPGKAPKLLIKYTSRLHSG
VPSRFSGSGSGTDFTLTISLQPEDFATYFCQQGYTLPWTFGGGTKVEIK

PL-02

VH (SEQ ID NO: 141):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQGLEWMGMIHPN
VGSTNYNEKFKSKATMTRDKSSSTVYMELSSLRSEDNAVYYCARSGYSSPYYFDY
WGQGTLVTVSS

VL (SEQ ID NO: 142):

DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLQSGV
PSRFSGSGSGTDFTFTISLQPEDATYFCQQGNTLPWTFGQGGTKVEIK

PL-03

VH (SEQ ID NO: 143):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQGLEWMGMIHPN
SGGNNYNEKFKSRVTMTRDTSISTAYMELSRRLRSDDNAVYYCARSWYGSSPYYFDY
WGQGTLVTVSS

VL (SEQ ID NO: 144):

DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLHSGV
PSRFSGSGSGTDFTFTISLQPEDATYFCQQGNTLPWTFGQGGTKVEIK

FIG. 6A

PL-04

VH (SEQ ID NO: 145):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQGLEWMGMIHPT
GVSTDYNEKFKSRVTMTRDTSTSTVYMELSSLRSEDNAVYYCARSDYGSSPYFDY
WGQGTLVTVSS

VL (SEQ ID NO: 146):

DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKAPKLLIKYTSRLHSGV
PSRFGSGSGTDFTLTISLQPEDFATYFCQQGDTLPWTFGGGTKVEIK

PL-05

VH (SEQ ID NO: 147):

DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWRQFPGNKLEWMGYISDSGS
TSYNPSLKSRISITRDTSKNQFFLQLNSVTTEDATYYCANSFLRLRSYFDHWGQGT
LTVSS

VL (SEQ ID NO: 148):

DIVMTQSHKFMSTSVGDRVSITCKASQDVNVAVAWYQQKPGQSPKLLIFWASTRHI
GVPDRFTGSGSGTDYTLTISSVQAEDLALYYCQQHYSTPYTFGGGTKLEIK

PL-06

VH (SEQ ID NO: 149):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGINWVRQAPGQRLEWMGWCIYIG
NDYTNYNEKFKGRVTITRDTASTAYMELSSLRSEDNAVYYCARAYYGSRVDYWG
QGTLVTVSS

VL (SEQ ID NO: 150):

DIQMTQSPSSLSAFVGDRVTITCKASQDINKYIAWYQQKPGKAPKLLIHYTSTLQPGV
PSRFGSGSGRDFTFITISLQPEDATYYCLQYDNLYTFGGGTKVEIK

PL-07

VH (SEQ ID NO: 151):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGINWVRQAPGQRLEWMGWCIYIG
NDYTNYNEKFKGRVTITRDTASTAYMELSSLRSEDNAVYYCARAYYGSRVDYWG
QGTLVTVSS

VL (SEQ ID NO: 152):

EIVLTQSPVTLSSLSPGERATLSCQSISDYLHWYLQKPGQAPRLLIKCASQSISGIPARFS
GSGSGSDFTLTISLQPEDFAVYYCQNGHSFPYTFGGGTKVEIK

FIG. 6B

PL-08

VH (SEQ ID NO: 153):

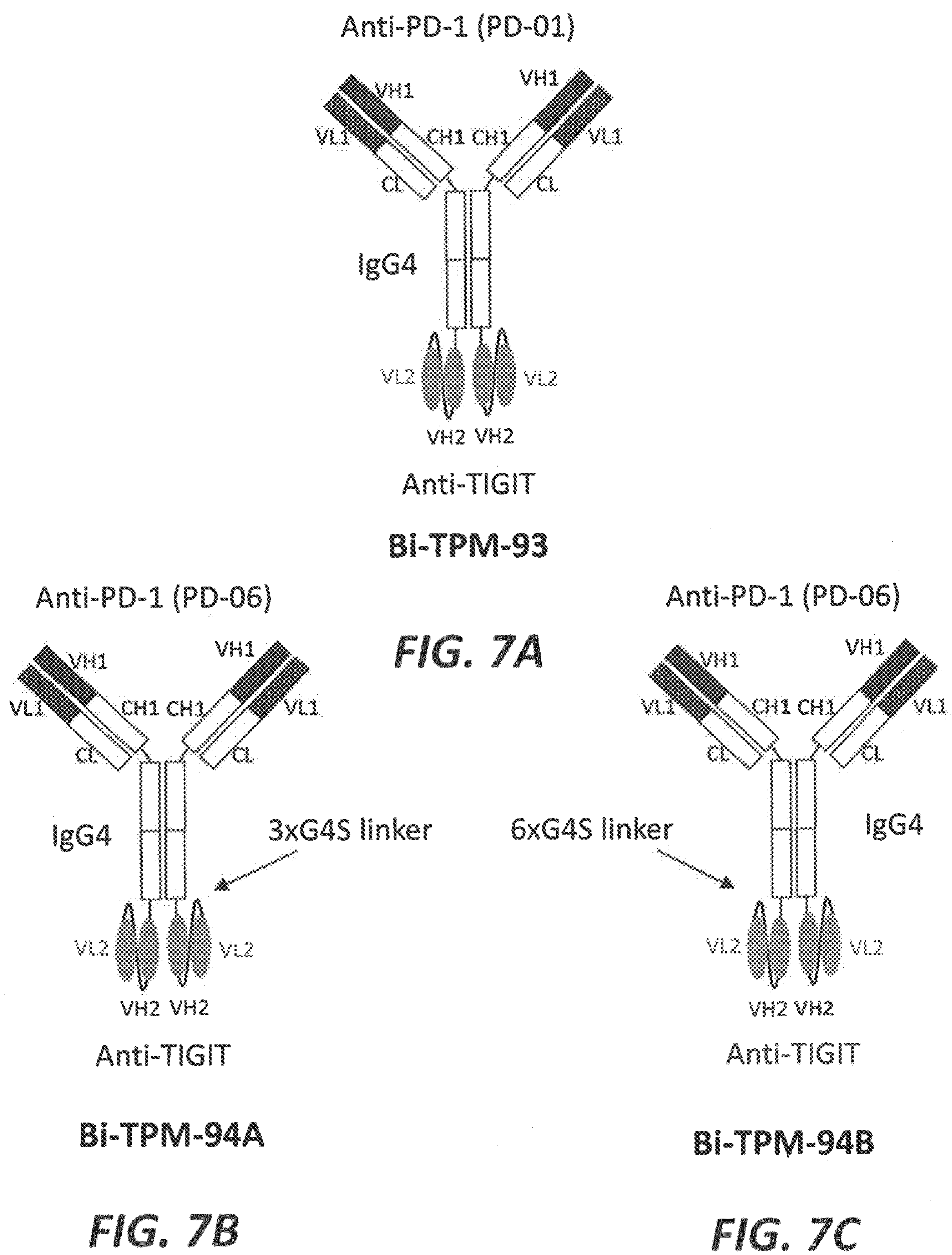
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQGLEWMGMIHPN
SGGNNYNEKFKSRVTMTRDTSISTAYMELSRLRSDDTAVYYCARSWYGSSPYFDY
WGQGTLVTVSS

VL (SEQ ID NO: 154):

DIQMTQSPSSLSASVGDRVTISCRASQDIDNYLNWYQQKPGKAPKLLIKYTSRLHSG
VPSRFSGSGSGTDFTLTISLQPEDFATYFCQQGYTLPWTFGGGTKVEIK

FIG. 6C

Anti-PD-1 antibodies with TIGIT scfv



Functional Domain Sequences in FIGs. 7A-7C

VH/VL or Fusion Protein Domain	Amino Acid Sequences of Functional Domains
Anti-PD-1 HCVR (PD-01)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFLMSWVRQAPGKGLEWVSTISGGGRDITYV DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKRTTYSMDYWGQGTSTVTVSS (SEQ ID NO:96)
Anti-PD-1 LCVR (PD-01)	DIQMTQSPSSVSASVGDRVITITCLASQTIGTWLAWYQQKPGKAPKLLIYAATSLADGVPSRFS GSGSGTDFLTITSSLPEDFATYYCQQFYSPWTFGGGTKLEIK (SEQ ID NO:97)
Anti-PD-1 HCVR (PD-06, 2P17)	QVQLVQSGAEVKKPGASVKVSCASGYTFTSYIHWVRQAPGQGLEWMGWIFPGSGNSKY NENFKGRVTLTADTSTSTVYMESSLRSEDVAVYYCASETYDYG DYWGQGT LVT VSS (SEQ ID NO:106)
Anti-PD-1 LCVR (PD-06, 2P17)	DIQMTQSPSFLSASVGDRVITITCKASQNVGTNVAWYQQKPGKAPKALIYSASYRSGVPSRFS GSGSGTEFTLTITSSLPEDFATYYCQQYYSYPYTFGQGTKLEIK (SEQ ID NO:107)
Anti-TIGIT HCVR (B21-35)	QVQLVQSGAEVKKPGASVKVSCASGYTFTSYMHVVRQAPGQGLEWMGIINPSGGRTSY AQMFQGRVTMTTRDTSTSTVYMESSLRSEDVAVYYCARDREEQWPVGGFDYWGQGT LVT V SS (SEQ ID NO:66)
Anti-TIGIT LCVR (B21-35)	DIQMTQSPSSLSASVGDRVITITCRASQSIIRRYLNWYQQKPGKAPKLLIYSASNLQSGVPSRFS GSGSGTDFLTITSSLPEDFATYYCQQSYIIPPTFGQGTKVEIK (SEQ ID NO:67)
IgG4 CH1-CH2-CH3 (hinged stabilized S231P)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHN HYTQKSLSLSLGK (SEQ ID NO: 155)
3xG4S linker	GGGGSGGGGSGGGGS (SEQ ID NO:188)
6xG4S linker	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO:191)

FIG. 8

HC and LC Sequences of Antagonists in FIGs. 7A-7C

Antagonist (HC/LC)	Amino Acid Sequence
Bi-TPM-93 HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFLMSWVRQAPGKGLEWVSTISGGG RDTYYVDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKRTTYSMDYWGQGT SVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKGGGGSGGGGS QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHVVRQAPGQGLEWMGIINPS GGRTSYAQMFGGRVTMTRDTSTSTVYMESSLRSEDTAVYYCARDREEQWPVGGF DYWGQGTLVTVSSGGGGSGGGSGGGGSDIQMTQSPSSLSASVGDRVITTCRASQ SIRRYLNWYQQKPGKAPKLLIYSASNLSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCQQSYIIPPTFGQGTKVEIK (SEQ ID NO: 158) (PD-01)
TPM-93 LC	DIQMTQSPSSVSASVGDRVITITCLASQTIGTWLAWYQQKPGKAPKLLIDAATSLADG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQFYSPWTFGGGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 159) (PD-01)
Bi-TPM-94A HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWMGWIFPG SGNSKYNENFKGRVTLTADTSTSTVYMESSLRSEDTAVYYCASETYDYG DYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKGGGGSGGGGS QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHVVRQAPGQGLEWMGIINPS GGRTSYAQMFGGRVTMTRDTSTSTVYMESSLRSEDTAVYYCARDREEQWPVGGF DYWGQGTLVTVSSGGGGSGGGSGGGGSDIQMTQSPSSLSASVGDRVITTCRASQ SIRRYLNWYQQKPGKAPKLLIYSASNLSGVPSRFSGSGSGTDFTLTISLQPEDFATY YCQQSYIIPPTFGQGTKVEIK (SEQ ID NO: 160)
Bi-TPM-94A LC	DIQMTQSPSFLSASVGDRVITITCKASQNVGTNVAWYQQKPGKAPKALIYSASYRSG VPSRFSGSGSGTEFTLTISLQPEDFATYYCQQYYSYPYTFGQGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 161)

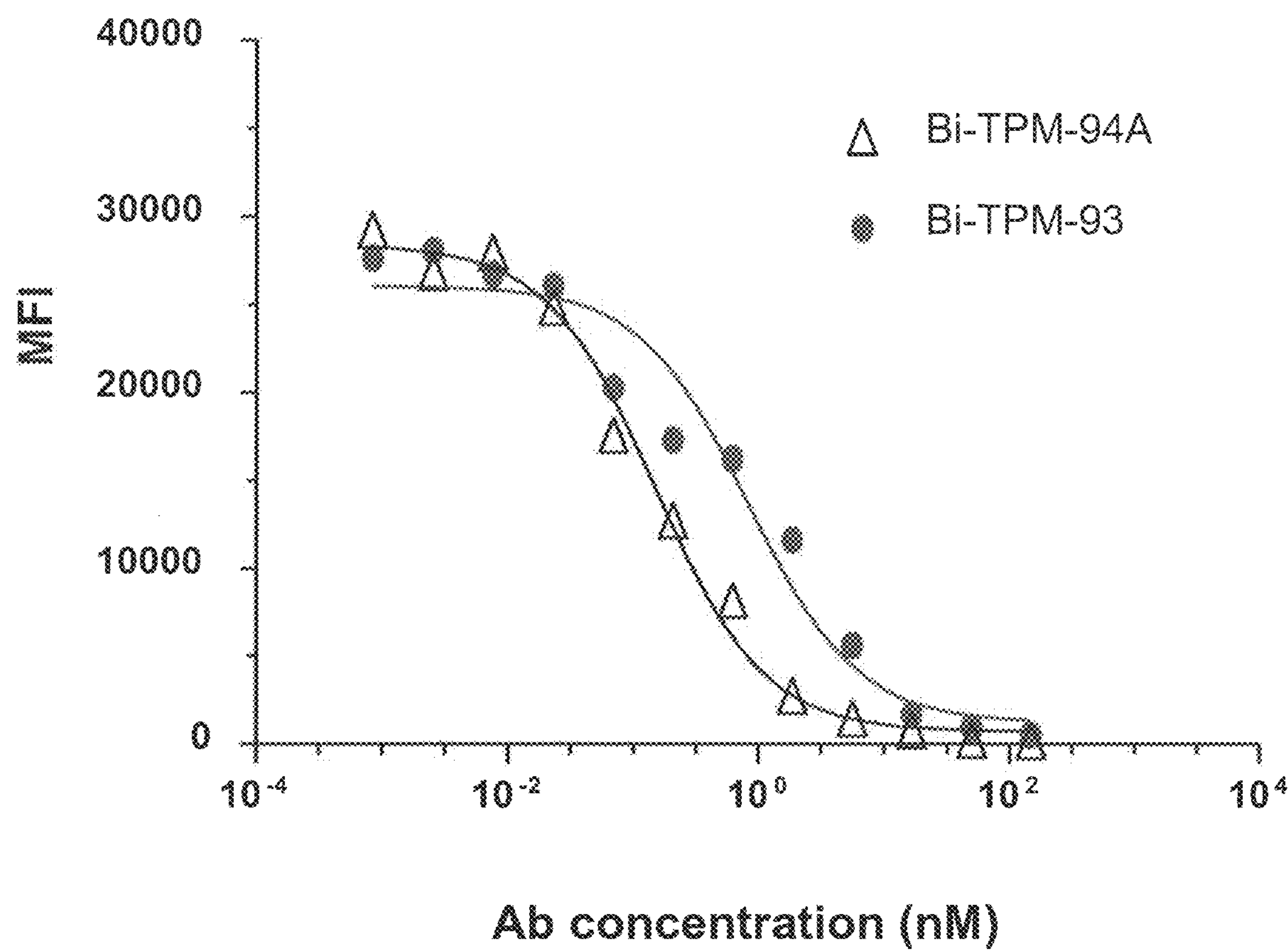
FIG. 9A

HC and LC Sequences of Antagonists in FIGs. 7A-7C

Antagonist (HC/LC)	Amino Acid Sequence
Bi-TPM-94B HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYIHWVRQAPGQGLEWMGWIFPG SGNSKYNENFKGRVTLTADTSTSTVYMELSSLRSEDТАVYYCASETYDYGDYWGGQT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDPHKPSNTKVDKRVESKYGPPCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLKGGGGSGGGGS QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHVVRQAPGQGLEWMGIINPS GGRTSYAQMFQGRVTMTRDTSTSTVYMELSSLRSEDТАVYYCARDREEQWPVGGF DYWGQGTЛVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSDIQMTQSPS SLSASVGDRVITCRASQSIRRYLNWYQKPKGKAPKLLIYSASNLQSGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQSYIIPPTFGQGTKVEIK (SEQ ID NO: 162)
Bi-TPM-94B LC	DIQMTQSPSFLSASVGDRVITCKASQNVGTNVAWYQKPKGKAPKALIYSASYRYSG VPSRFSGSGSGTEFTLTISLQPEDFATYYCQQYYSYPYTFGQGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 161)

FIG. 9B

Bi-TPM-94A is a more potent
blocker of PD-1 than Bi-TPM-93



Molecule	IC50 (nM)
Bi-TPM-93	0.83
Bi-TPM-94A	0.15

FIG. 10

Robust transient expression levels for Bi-TPM-94B

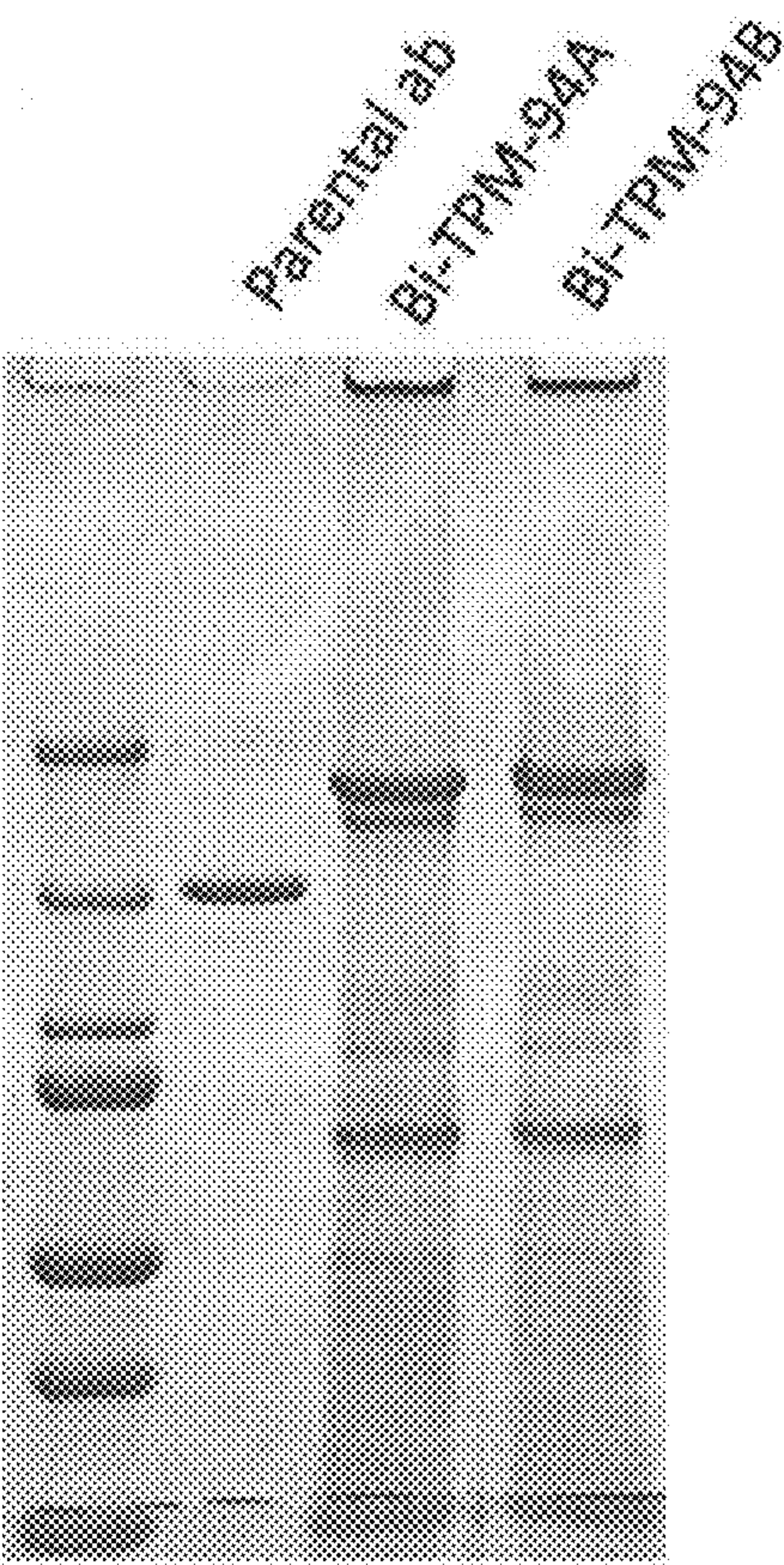


FIG. 11

Size-exclusion ultra-high performance liquid chromatography revealed species heterogeneity in Bi-TPM-93 and Bi-TPB-94A, which was eliminated by linker modification in Bi-TPM-94B

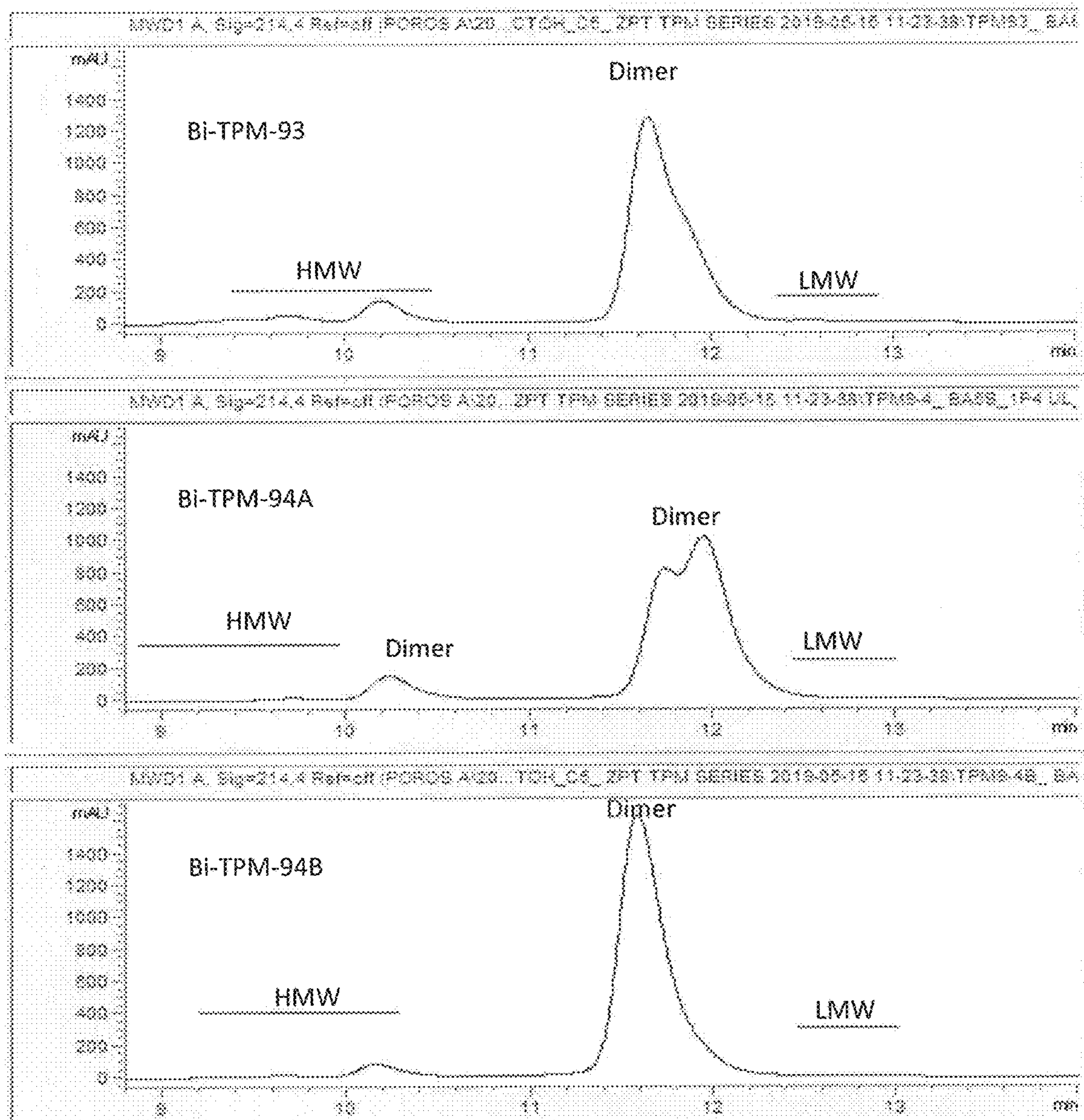
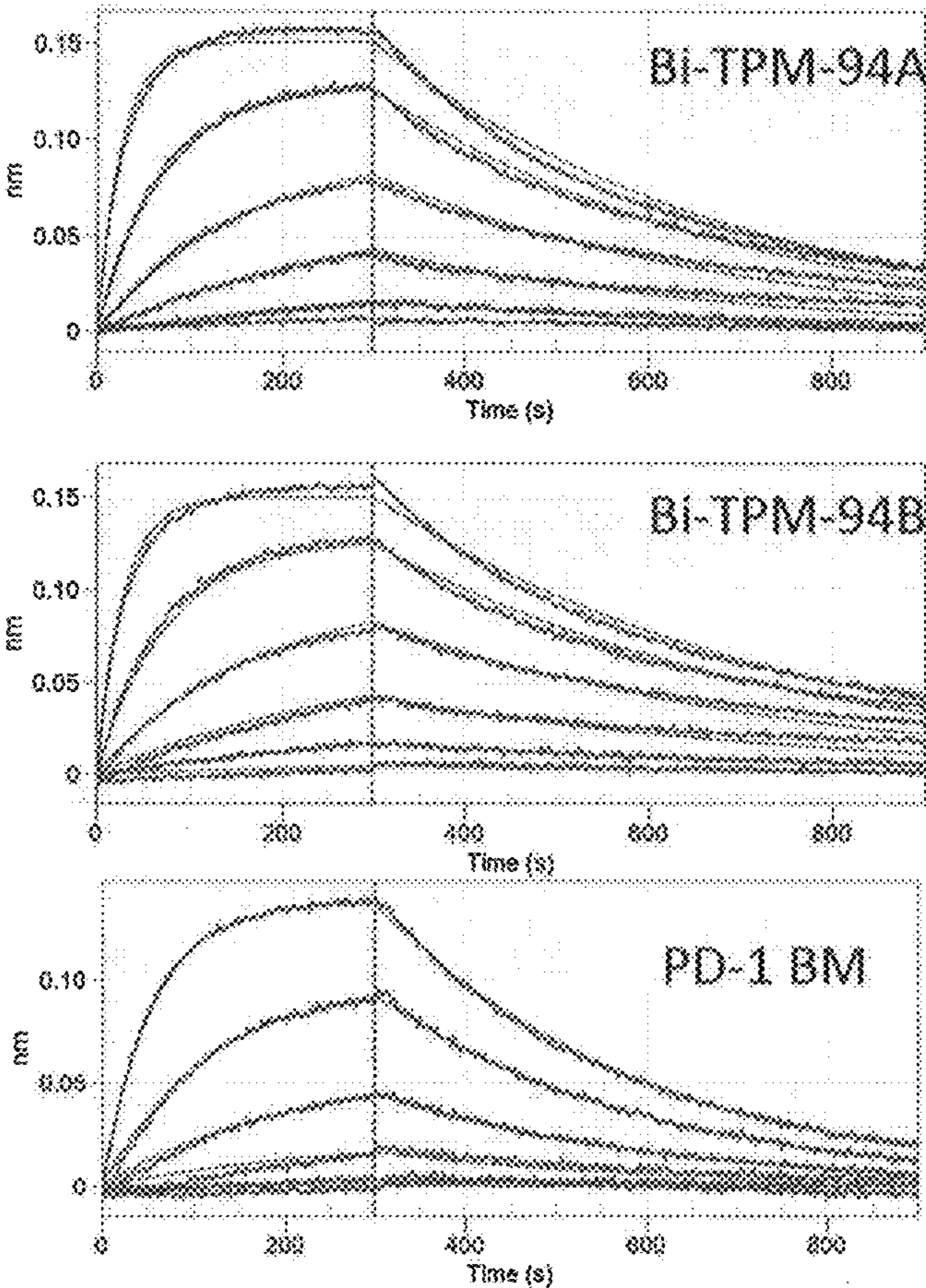


FIG. 12

Bi-TPM-94A and -94B bind PD-1 better than the benchmark Ab

PD-1
binding

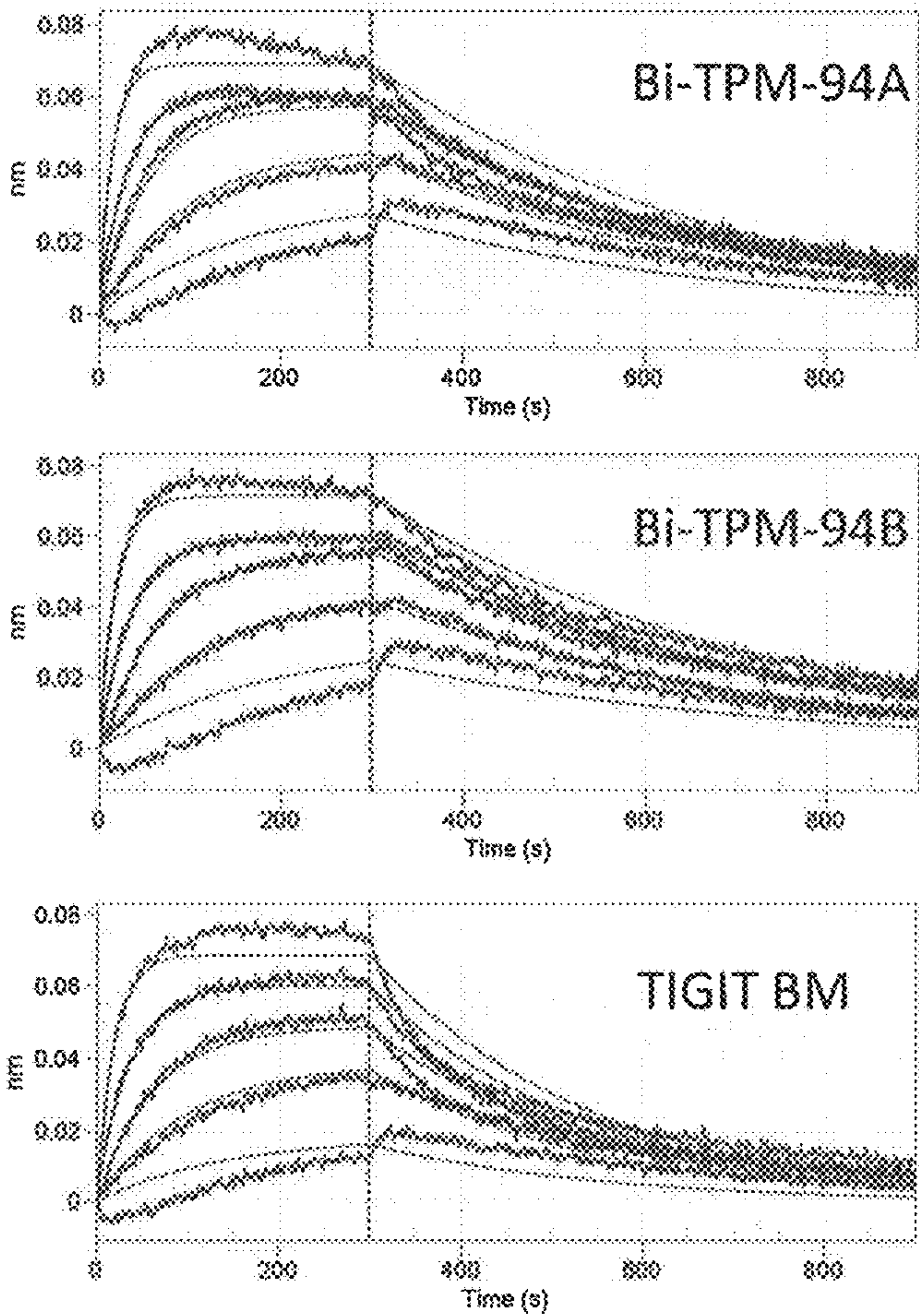


Antibody	Soluble Human PD-1		
	K_D (nM)	K_a ($M^{-1}s^{-1}$)	K_d (s^{-1})
Bi-TPM-94A	2.9	4.37E+05	1.27E-03
Bi-TPM-94B	2.7	4.11E+05	1.10E-03
PD-1 benchmark	8.8	1.88E+05	1.66E-03

FIG. 13A

Bi-TPM-94A and -94B bind TIGIT better than the benchmark Ab

TIGIT
binding



Antagonist	Soluble Human TIGIT		
	K_D (nM)	K_a ($M^{-1}s^{-1}$)	K_d (s^{-1})
Bi-TPM-94A	1.5	1.80E+06	2.71E-03
Bi-TPM-94B	1.7	1.35E+06	2.33E-03
TIGIT Benchmark	3.1	1.34E+06	4.11E-03

FIG. 13B

Bi-TPM-94A and Bi-TPM-94B potently block both PD1 and TIGIT binding to their ligands

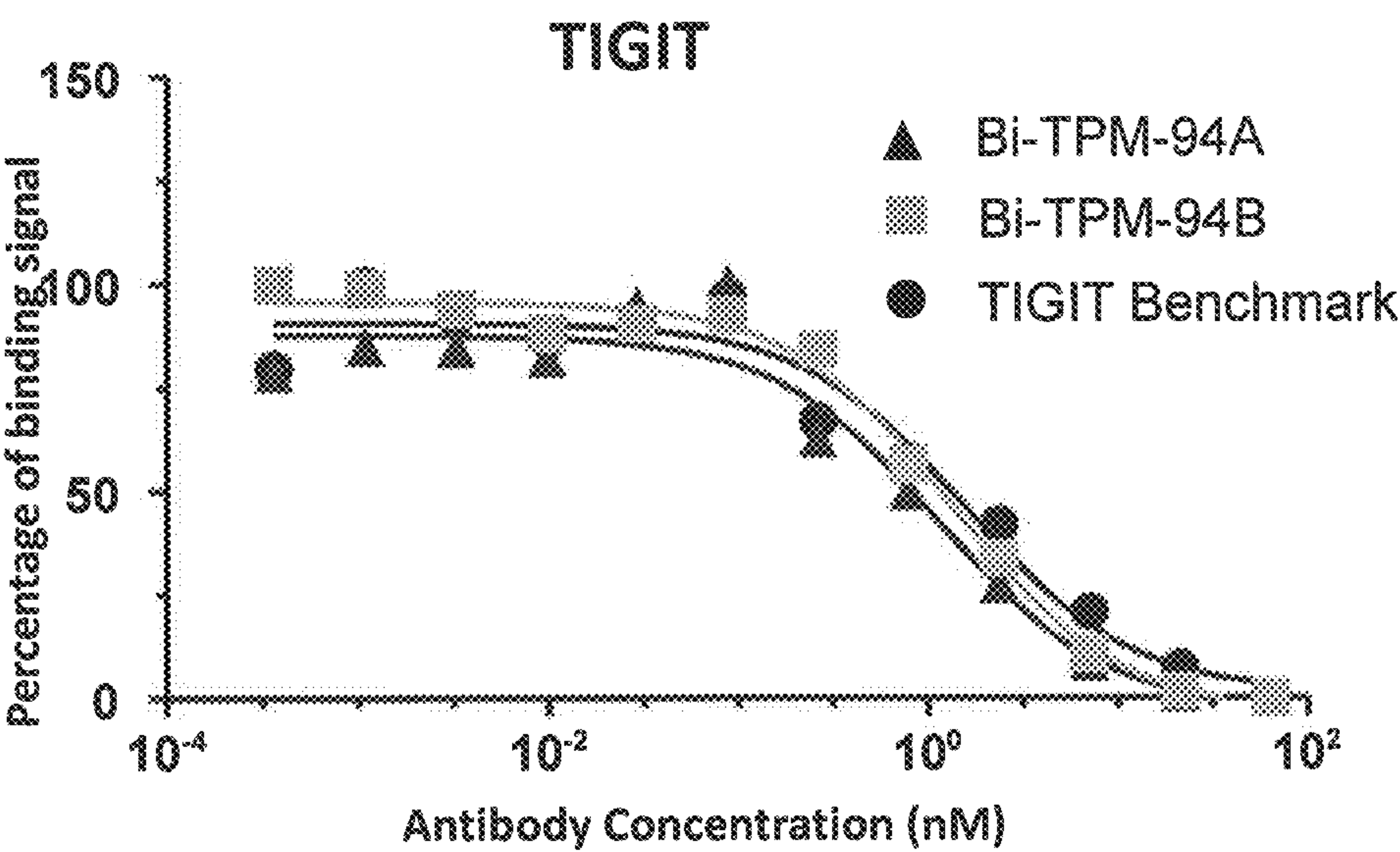


FIG. 14A

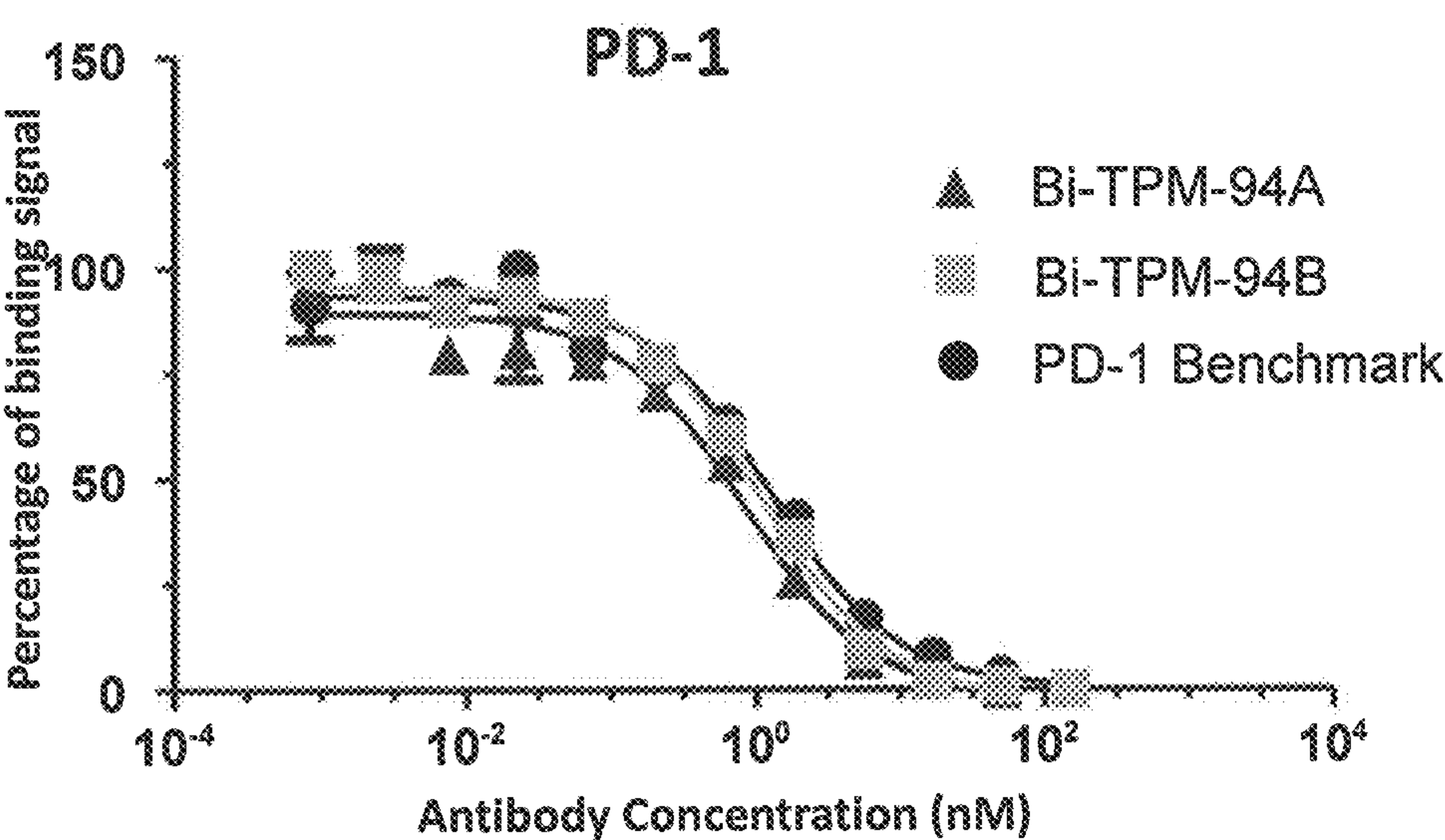


FIG. 14B

Bi-TPM-94A and Bi-TPM-94B can simultaneously,
bind both PD-1 and TIGIT

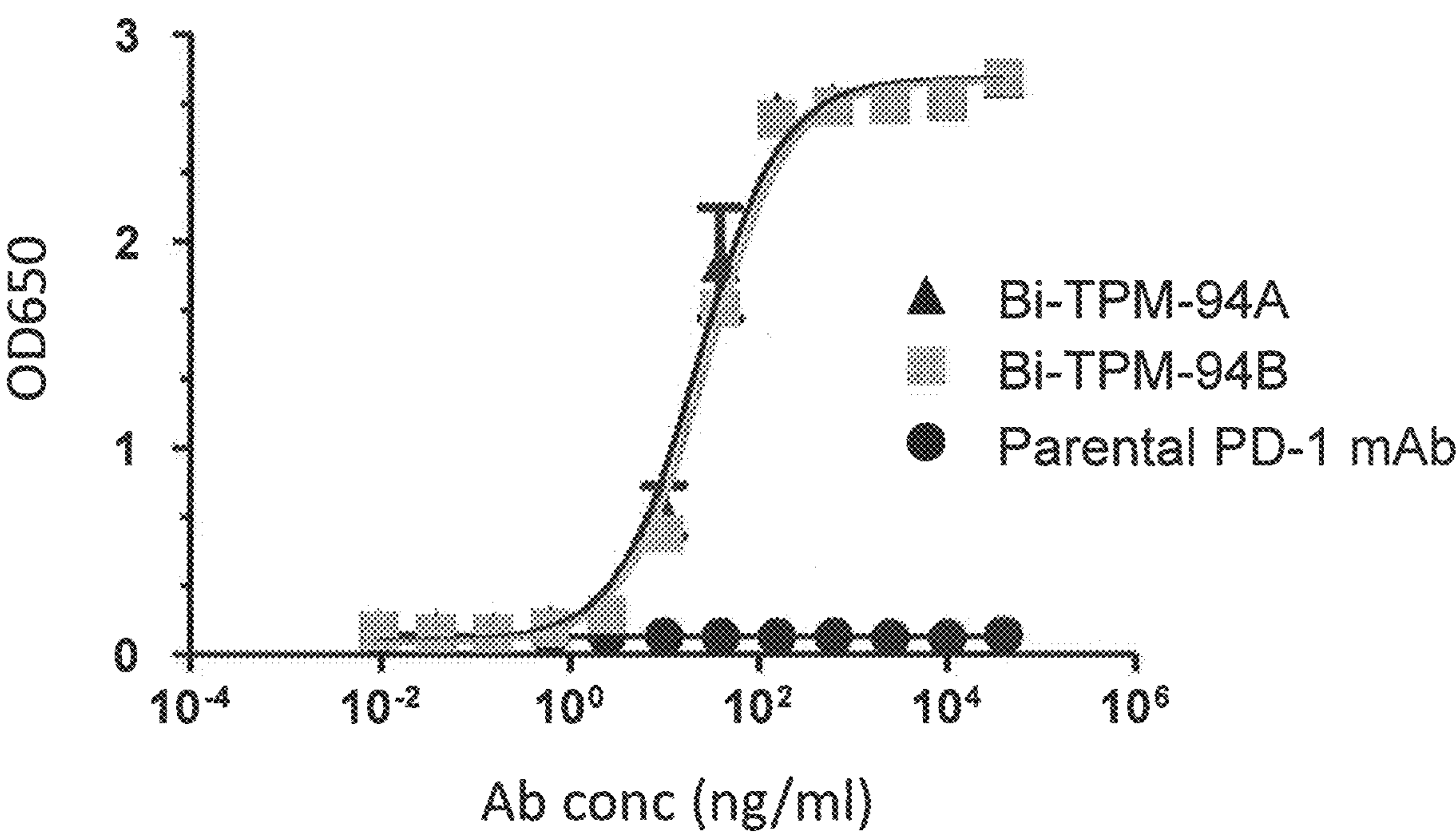


FIG. 15

Bi-TPM-94B induces more IFN- γ production than the individual combination of antibodies during CMV recall response of human PBMCs

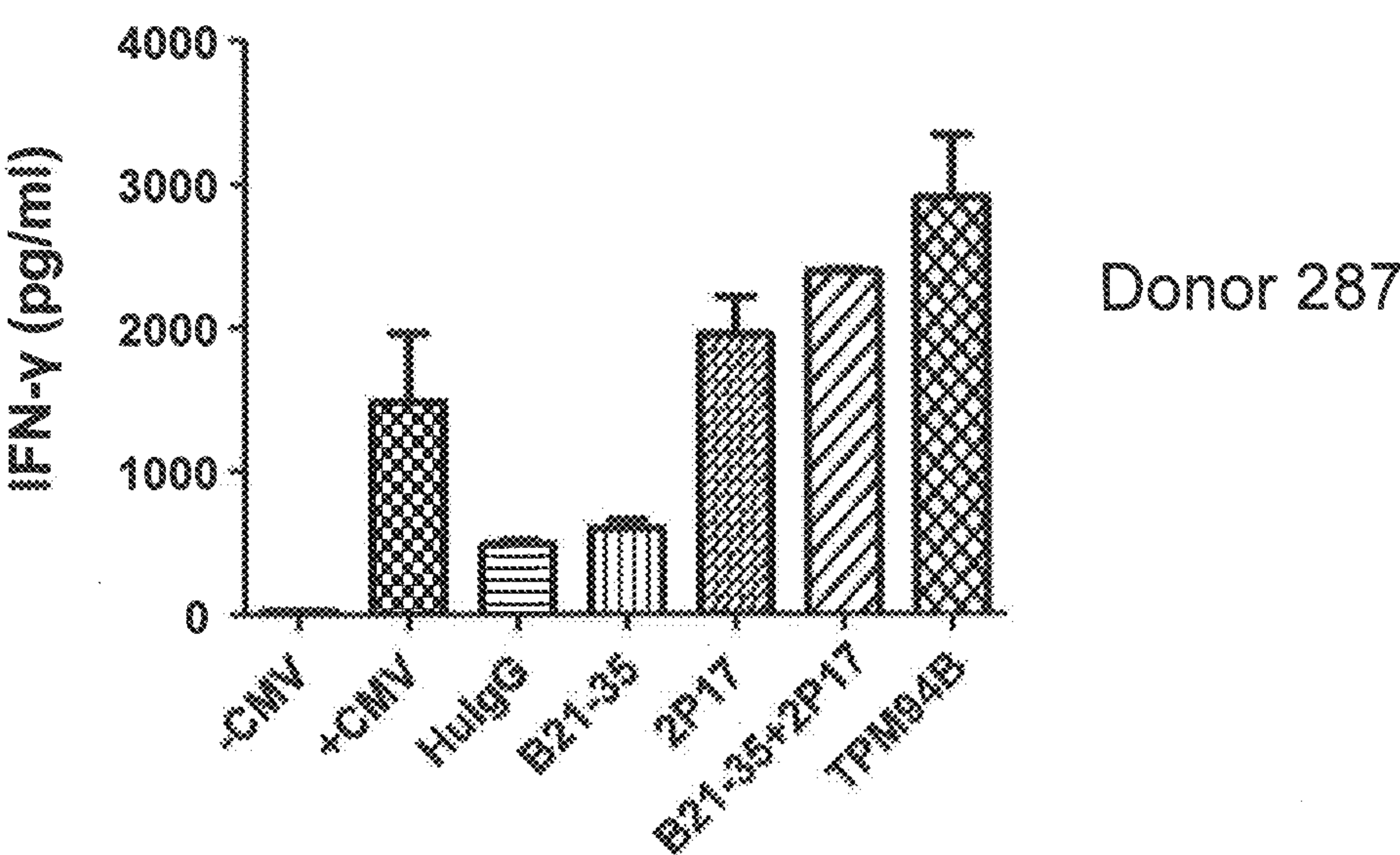


FIG. 16A

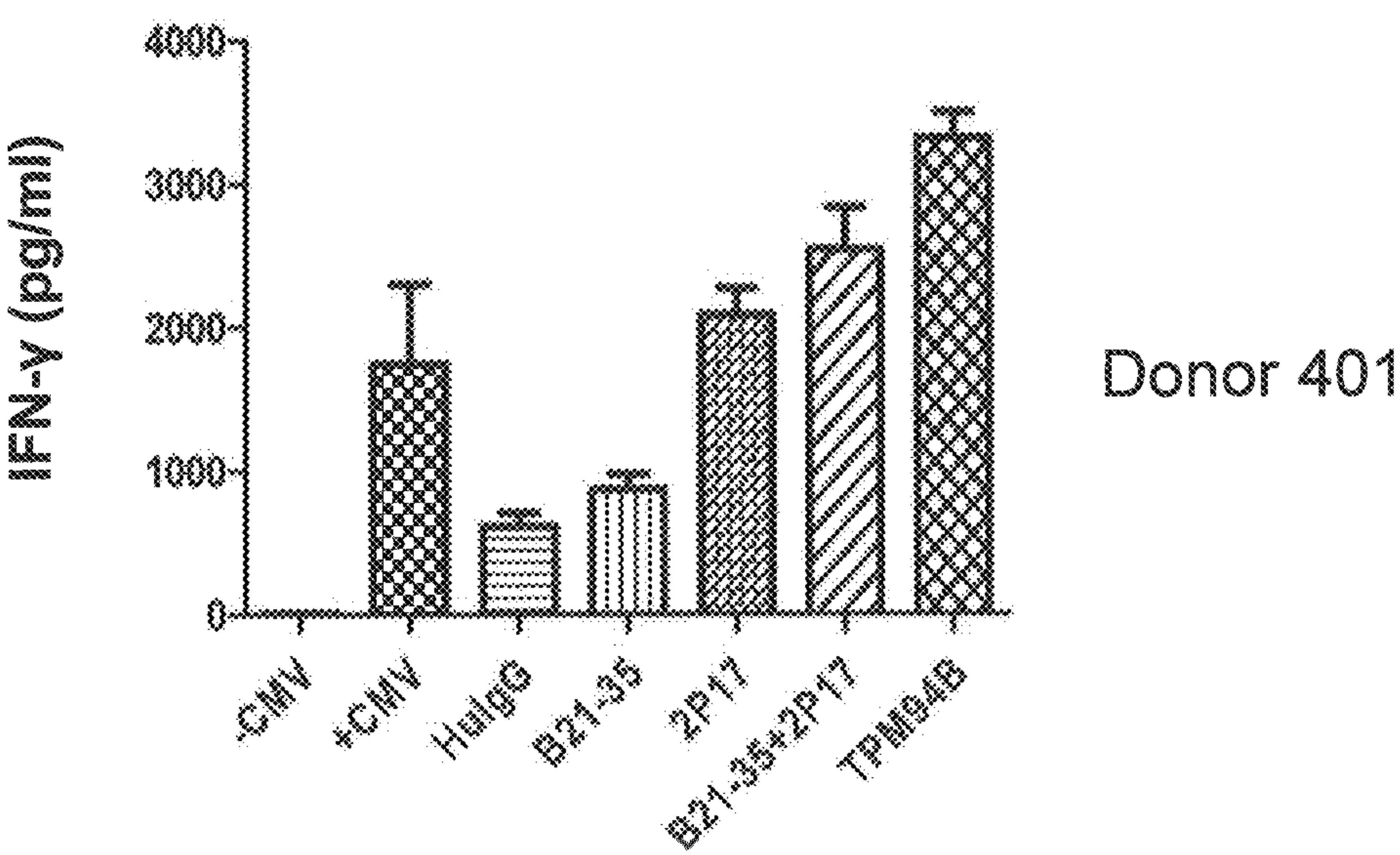
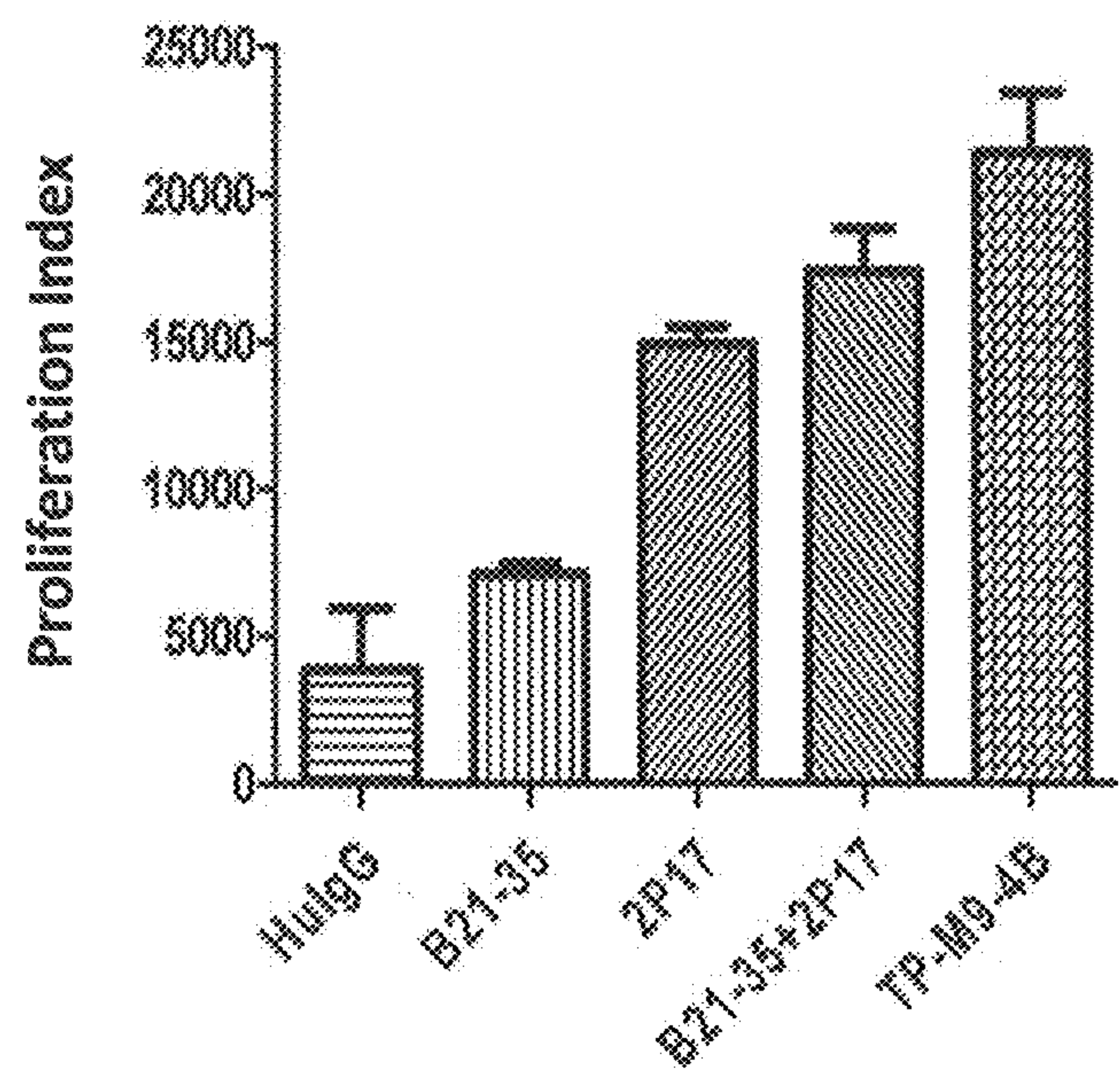


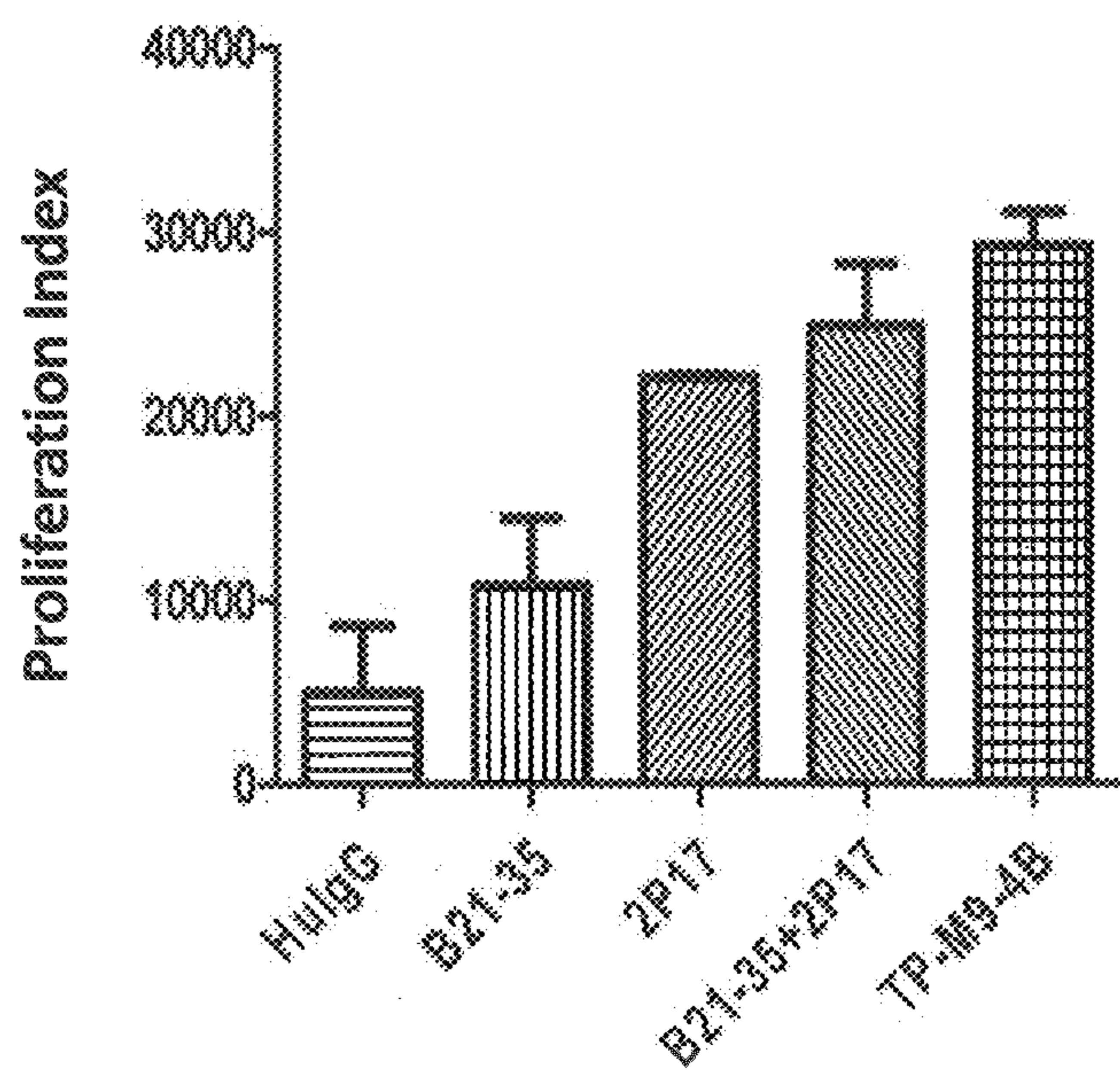
FIG. 16B

Bi-TPM94B induces more T cell proliferation than the combination of antibodies during CMV recall response of human PBMCs



Donor 287

FIG. 17A



Donor 401

FIG. 17B

Bi-TPM-94A and Bi-TPM-94B pharmacokinetics in mice

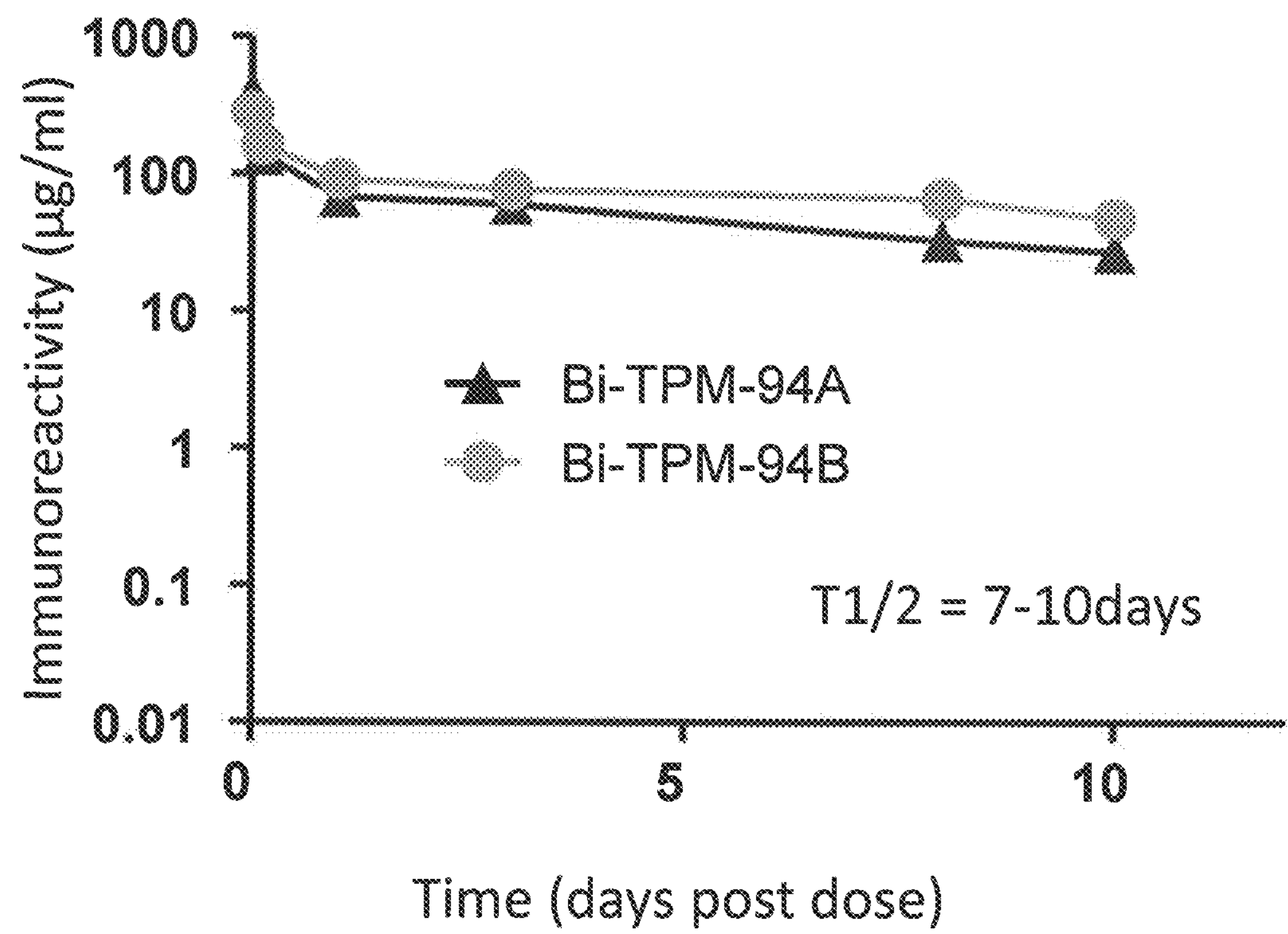


FIG. 18

Anti-LAG-3 mAb CDR1, CDR2 and CDR3 Amino Acid Sequences

mAb	HCDR1	HCDR2	HCDR3
2L2A.1	DYYMN (SEQ ID:163)	VINPYNGDTSYNQKFKG (SEQ ID:164)	DDGYVHYFDY (SEQ ID:165)
2L2A.6	DYYMN (SEQ ID:163)	VINPYNGDTSYNQKFKG (SEQ ID:164)	DDGYVHYFDY (SEQ ID:165)
2L27B	HYYMN (SEQ ID:166)	LINPYNGDTAYNQKFKD (SEQ ID:167)	TRDDGYVEH (SEQ ID:168)
3L1A	TAYTIH (SEQ ID:169)	WLYPGNDNIMYNENFKD (SEQ ID:170)	HEDWGPLDY (SEQ ID:171)

FIG. 19A

mAb	LCDR1	LCDR2	LCDR3
2L2A.1	RASQDISSRLT (SEQ ID:172)	ATSSLDS (SEQ ID:173)	LQYASSPLT (SEQ ID:174)
2L2A.6	RASQDISSRLT (SEQ ID:172)	ATSSLDS (SEQ ID:173)	LQYASSPLT (SEQ ID:174)
2L27B	RASQDIGSRLN (SEQ ID:175)	ATSSLDS (SEQ ID:173)	LQYASSPPT (SEQ ID:176)
3L1A	RASQSISS (SEQ ID:177)	RASNLES (SEQ ID:178)	QQSNGLPYT (SEQ ID:179)

FIG. 19B

Anti-LAG-3 mAb Variable Domain Sequences

2L2A.1

VH (SEQ ID NO: 180)

QVQLVQSGAEVKKPGASVKVSCKASGYTLTDYYMNWMRQAPGQGLEWMGVINPYNGDTSYNQKFKG
RVTMTRDTSTSTVYMELSSLRSEDTAVYYCVRDDGYVHYFDYWGGTLTVSS

VL (SEQ ID NO: 181)

DIQMTQSPSSLSASVGDRVTITCRASQDISSRLTWLQQEPEKAPKRLIYATSSLD SGV PKRFSGSGSGTDFTL
TISSLQPEDFATYYCLQYASSPLTFGGGTKVEIK

2L2A.6

VH (SEQ ID NO: 182)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMNWVRQAPGQGLEWMGVINPYNGDTSYNQKFKGR
VTMTRDTSTSTVYMELSSLRSEDTAVYYCARD DGYVHYFDYWGGTLTVSS

VL (SEQ ID NO: 183)

DIQMTQSPSSLSASVGDRVTITCRASQDISSRLTWLQQKPGKAPKRLIYATSSLD SGV PSRFSGSGSGTDFTL
TISSLQPEDFATYYCLQYASSPLTFGGGTKVEIK

2L27B

VH (SEQ ID NO: 184)

QVQLVQSGAEVKKPGASVKVSCKASGFTFSHYMNWVRQAPGQGLEWMGLINPYNGDTAYNQKFKDR
VTMTRDTSTSTVYMELSSLRSEDTAVYFCTRDDGYVVEHFDYWDDGYVVEHFDYWGGTLTVSS

VL (SEQ ID NO: 185)

DIQMTQSPSSLSASVGDRVTITCRASQDIGSRLNWYQQKPGKAPKRLIYATSSLD SGV PSRFSGSGSGTDFT
LTISSLQPEDFATYYCLQYASSPPTFGGGGTKVEIK

3L1A

VH (SEQ ID NO: 186)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYTIHWVRQAPGQGLEWMGWLYPGNDNIMYNENFKDR
VTMTRDTSTSTVYMELSSLRSEDTAVYYCARHEDWGPLDYWGQGT LTVSS

VL (SEQ ID NO: 187)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYRASNLESGVPSRFSGSGSGTEFTL
TISSLQPDDFATYYCQQSNGLPYTFGQGTKLEIK

FIG. 20

Mouse anti-LAG-3 mAbs block the interaction between LAG-3 and its MHC II ligand

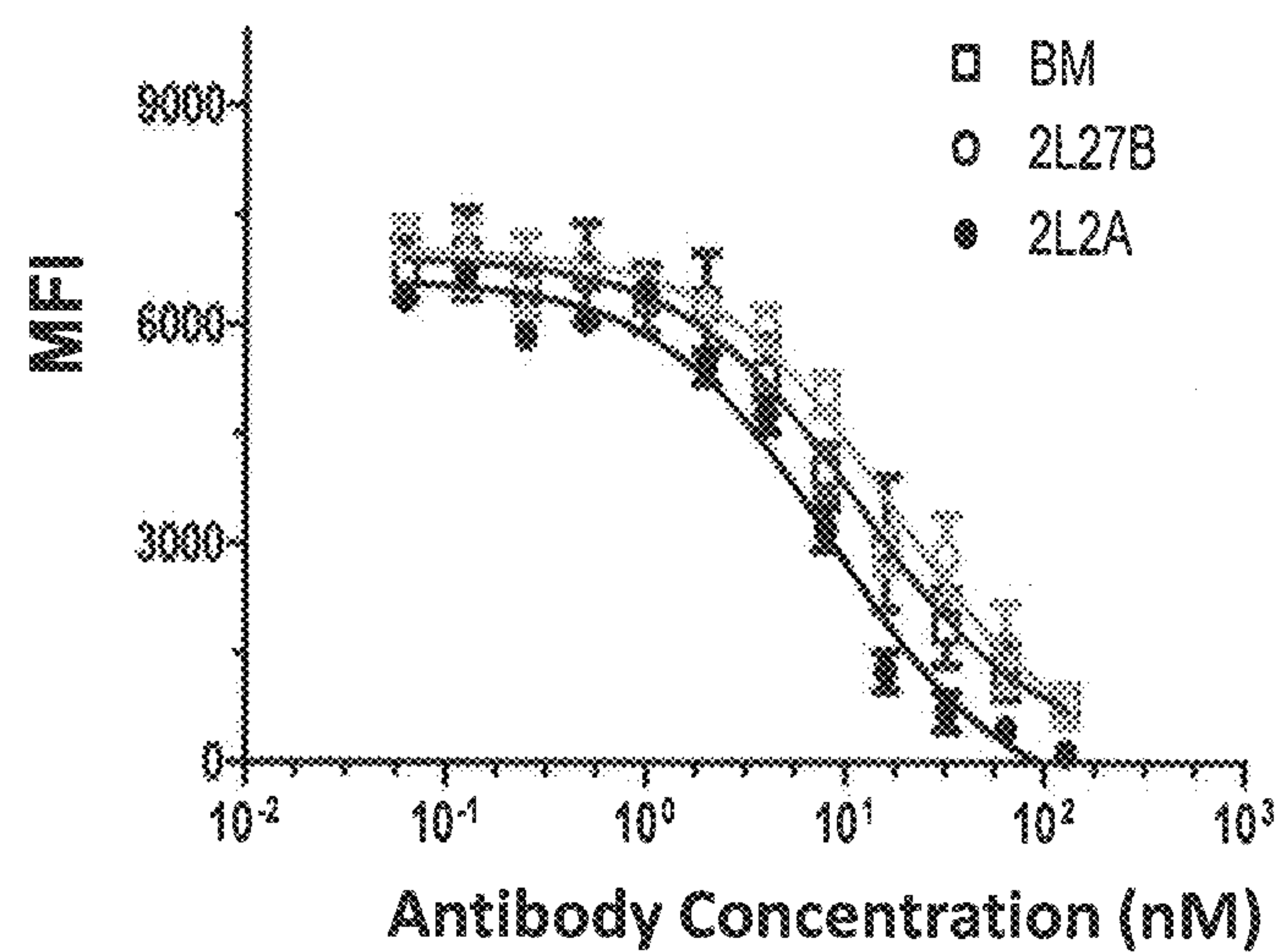


FIG. 21A

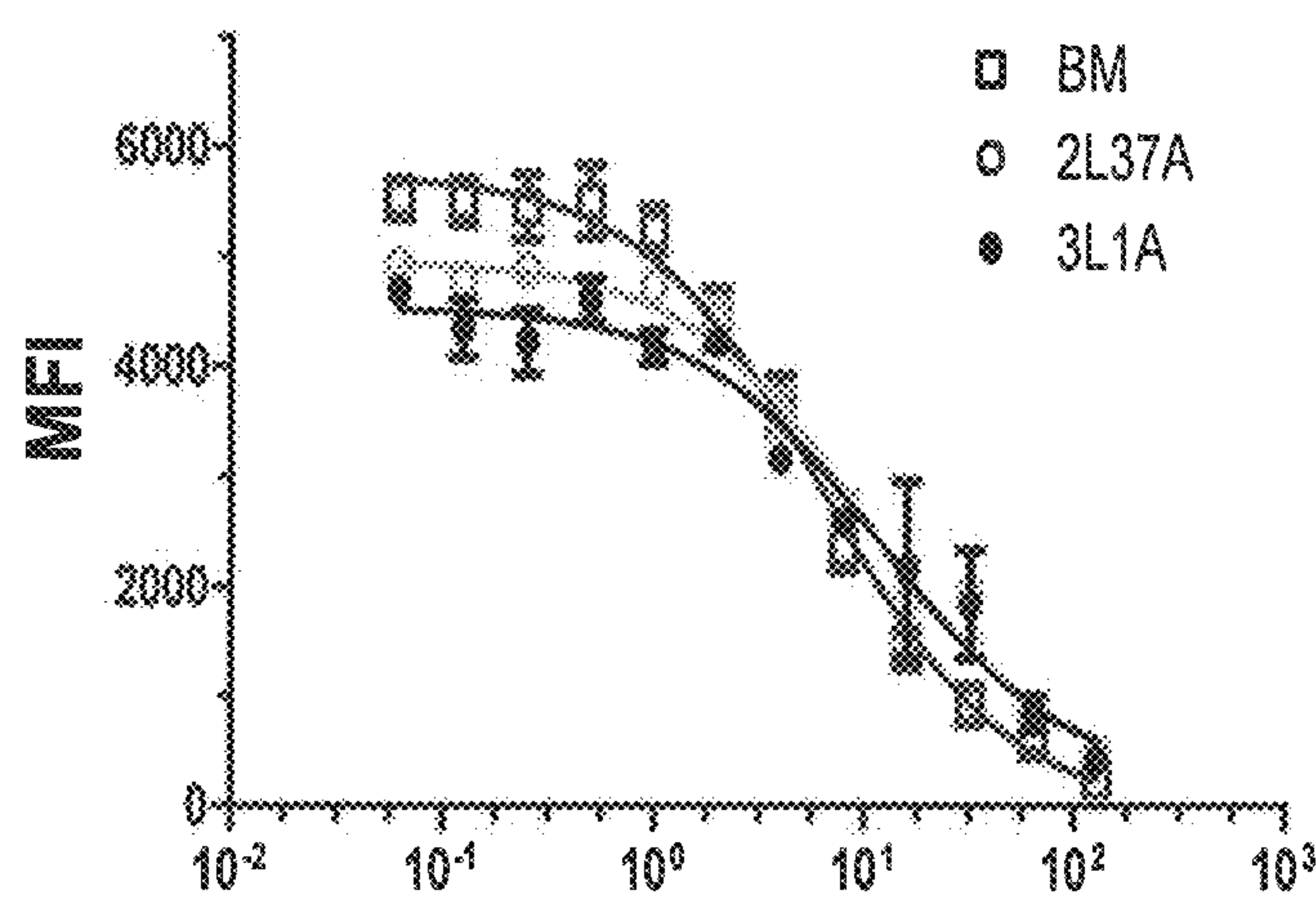
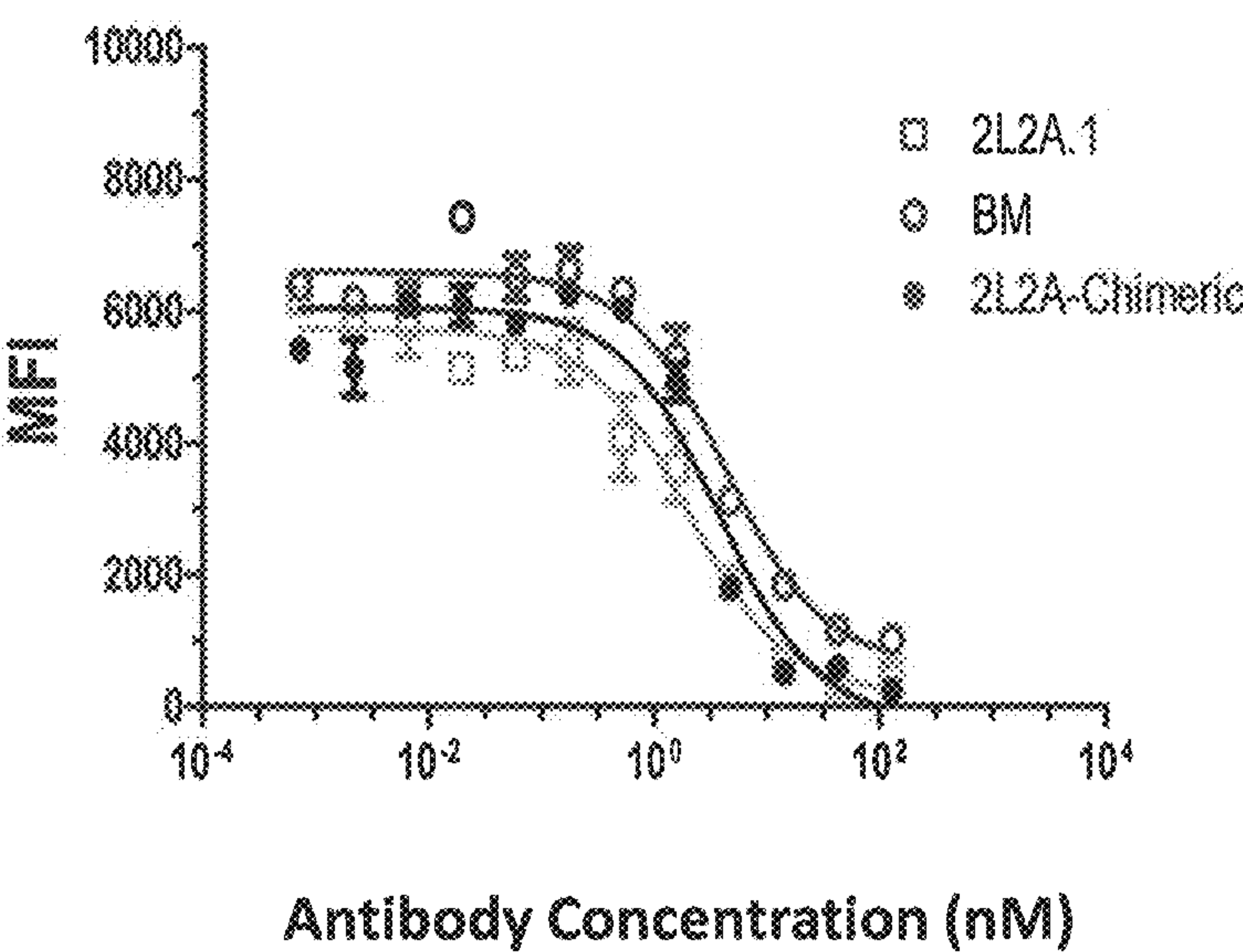


FIG. 21B

The humanized anti-LAG-3 2L2A.1 mAb is a better blocker than the benchmark (BM)



Antibody	IC50 (nM)
2L2A.1	1.97
Benchmark	4.14
2L2A- Chimeric	3.74

FIG. 22

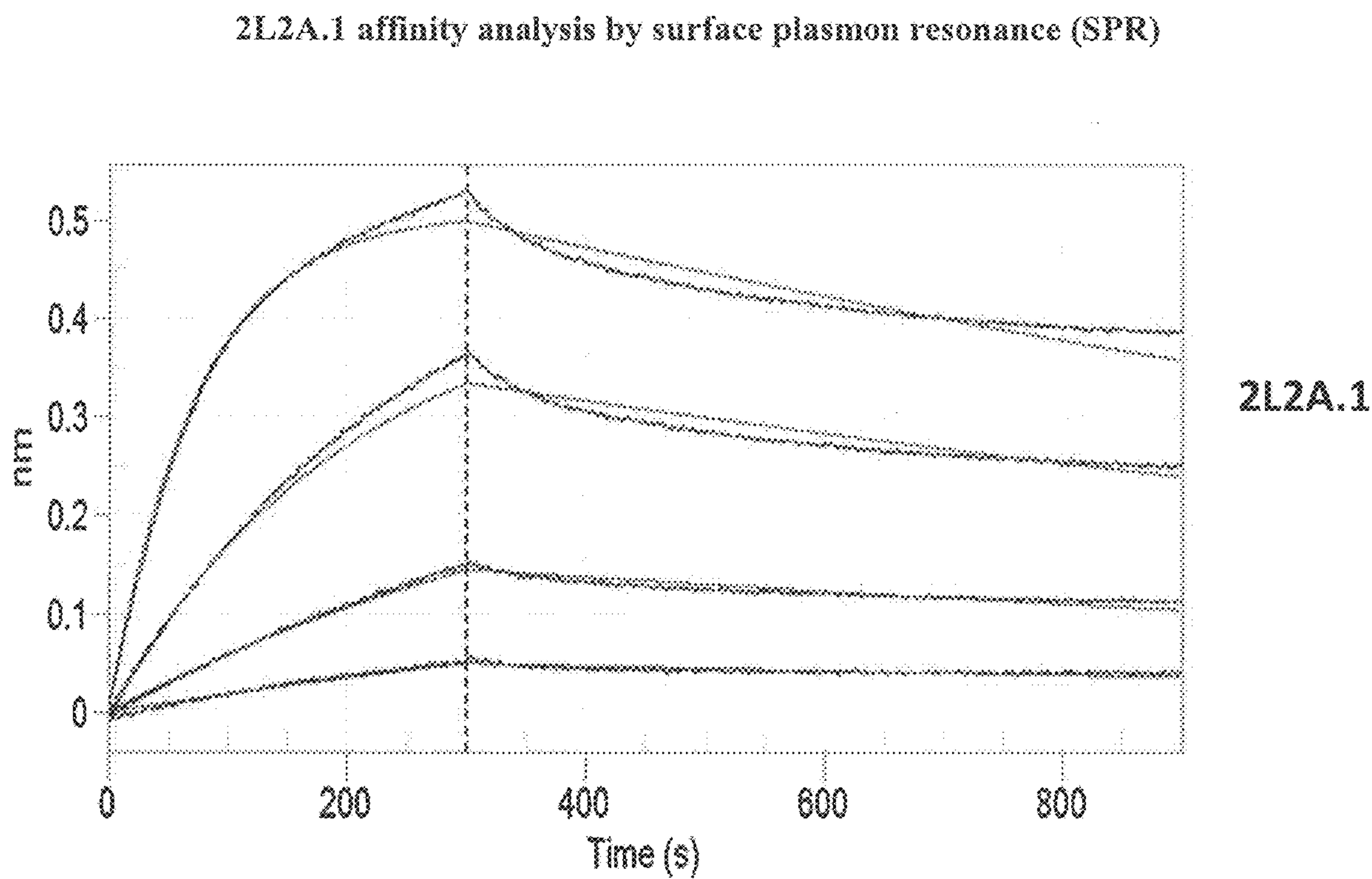
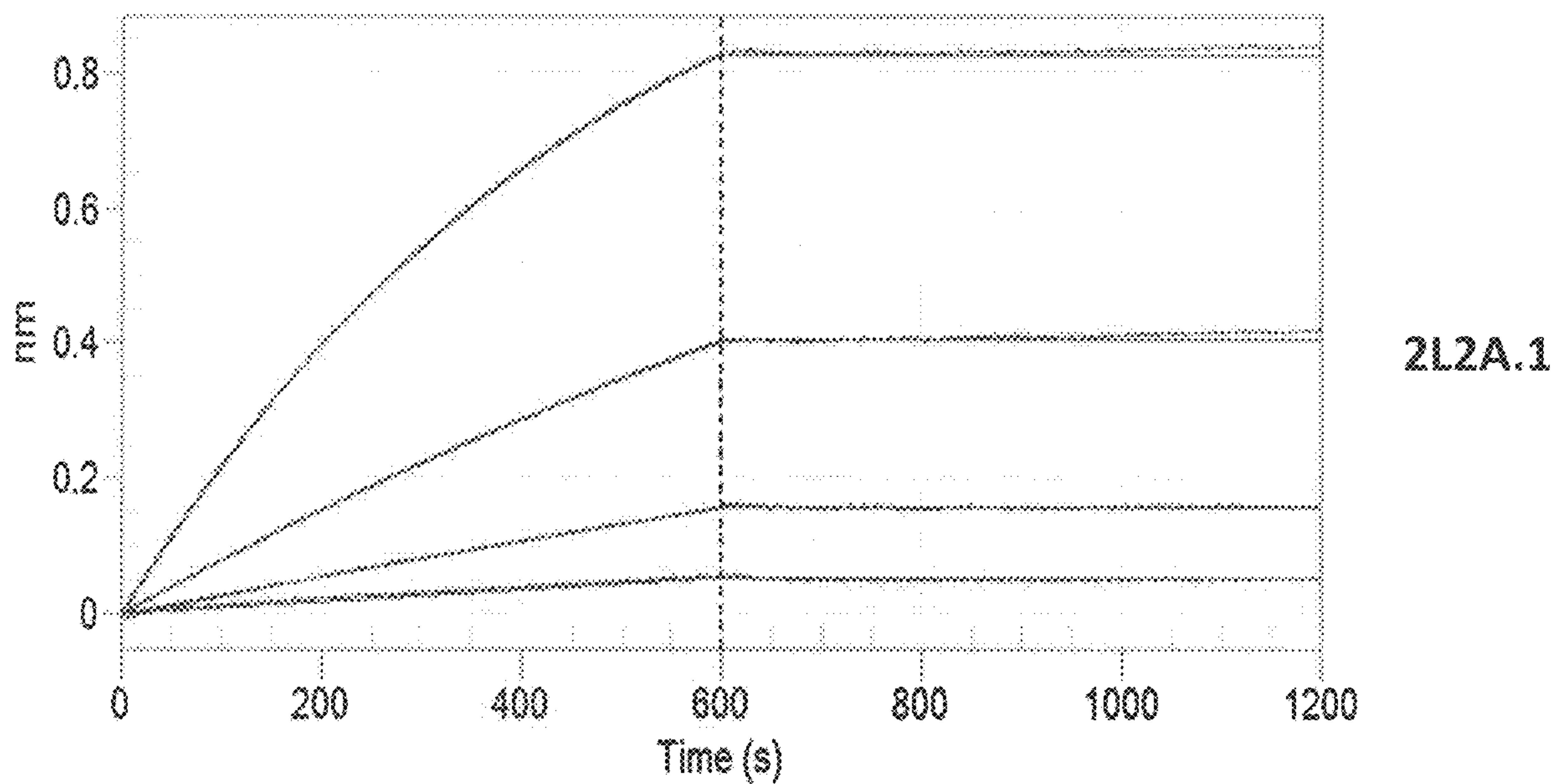


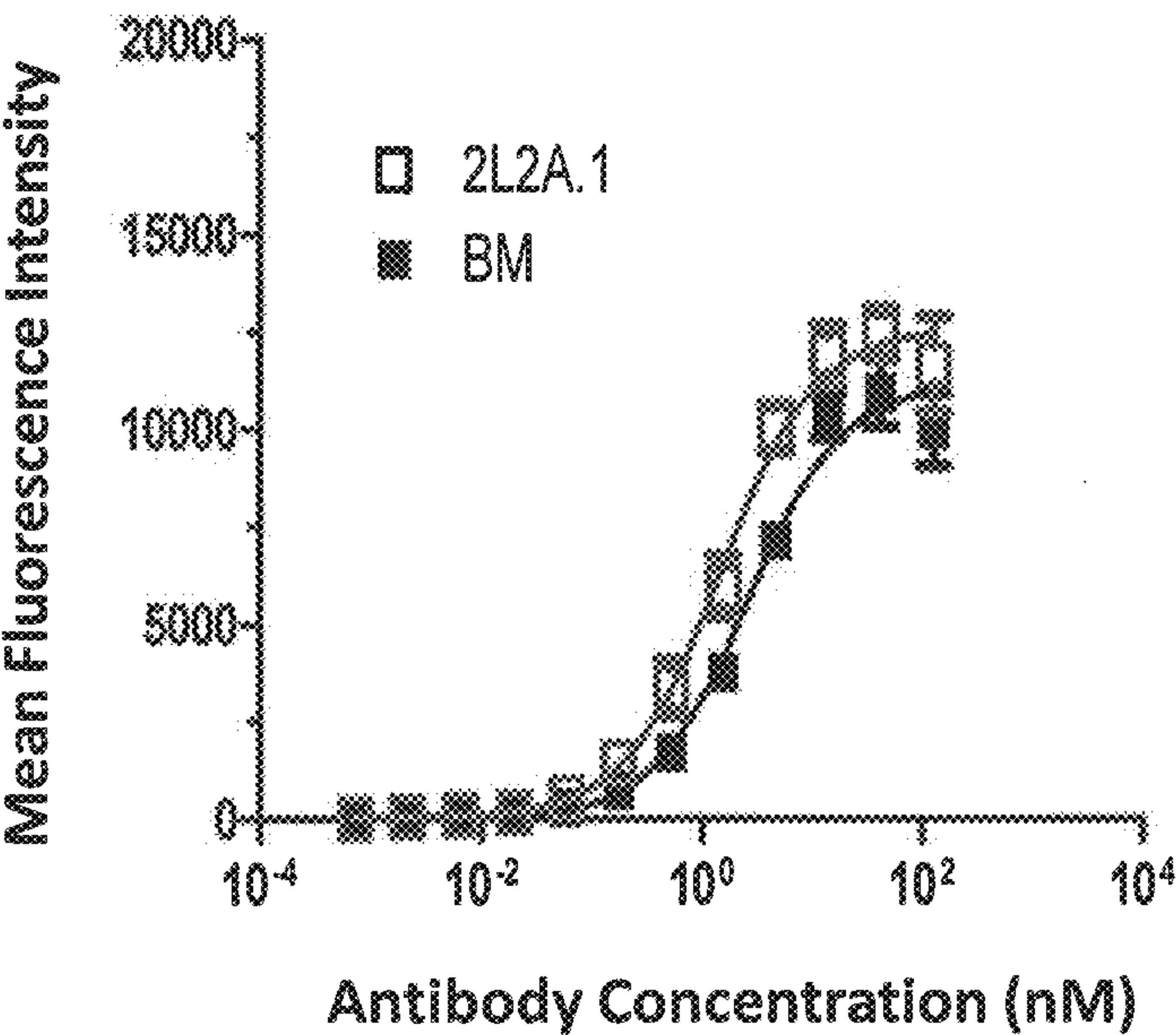
FIG. 23A



huLAG-3-mIgG2a			
Antibody	K_D (pM)	K_a ($M^{-1}s^{-1}$)	K_d (s^{-1})
2L2A.1	1 (± 11)	8.49E+04	<1.0E-07

FIG. 23B

2L2A.1 binding to LAG-3



Antibody	EC50 (nM)
Benchmark Ab	2.64
2L2A.1	1.48

FIG. 24

2L2A.1 expression

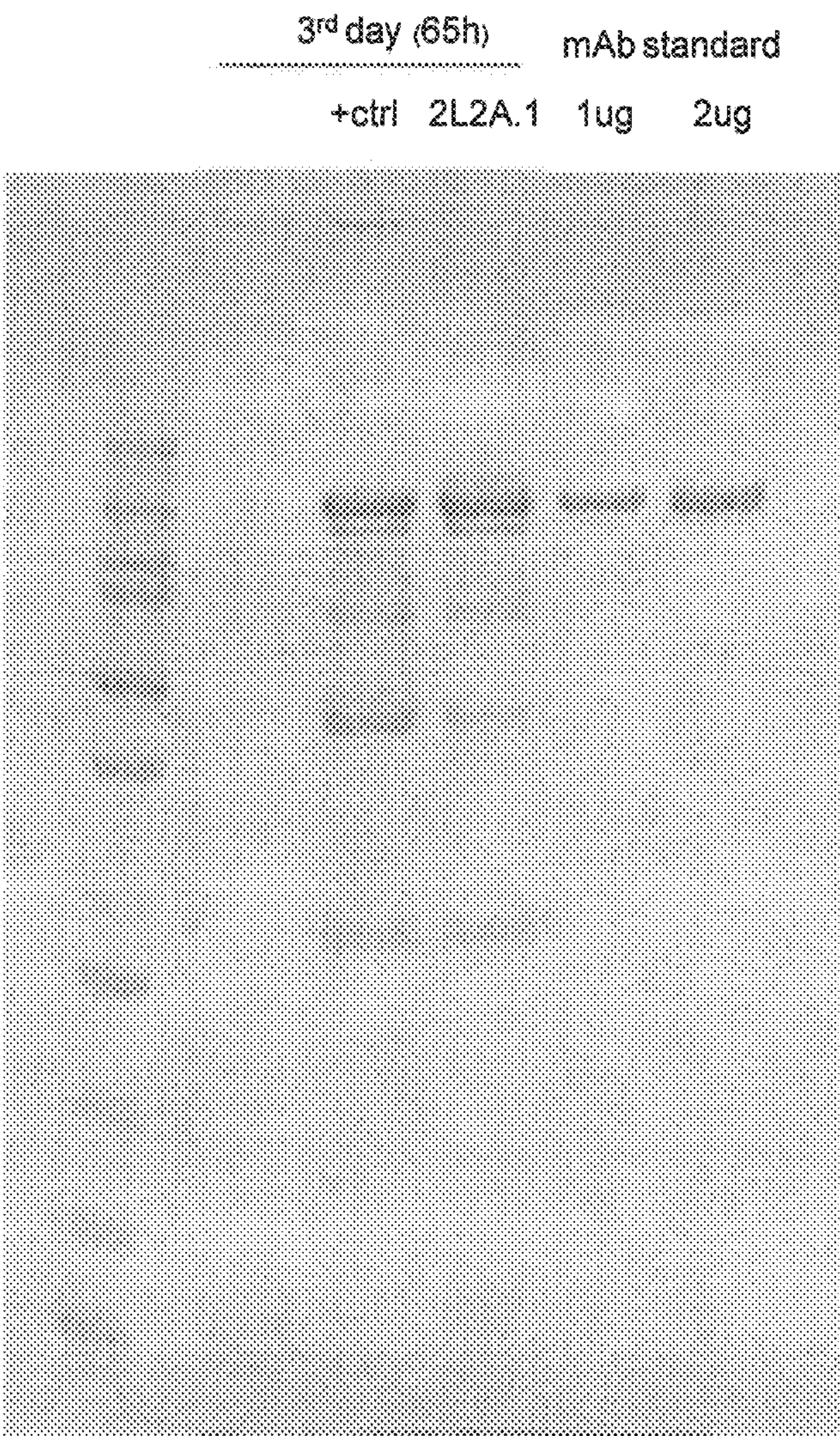


FIG. 25

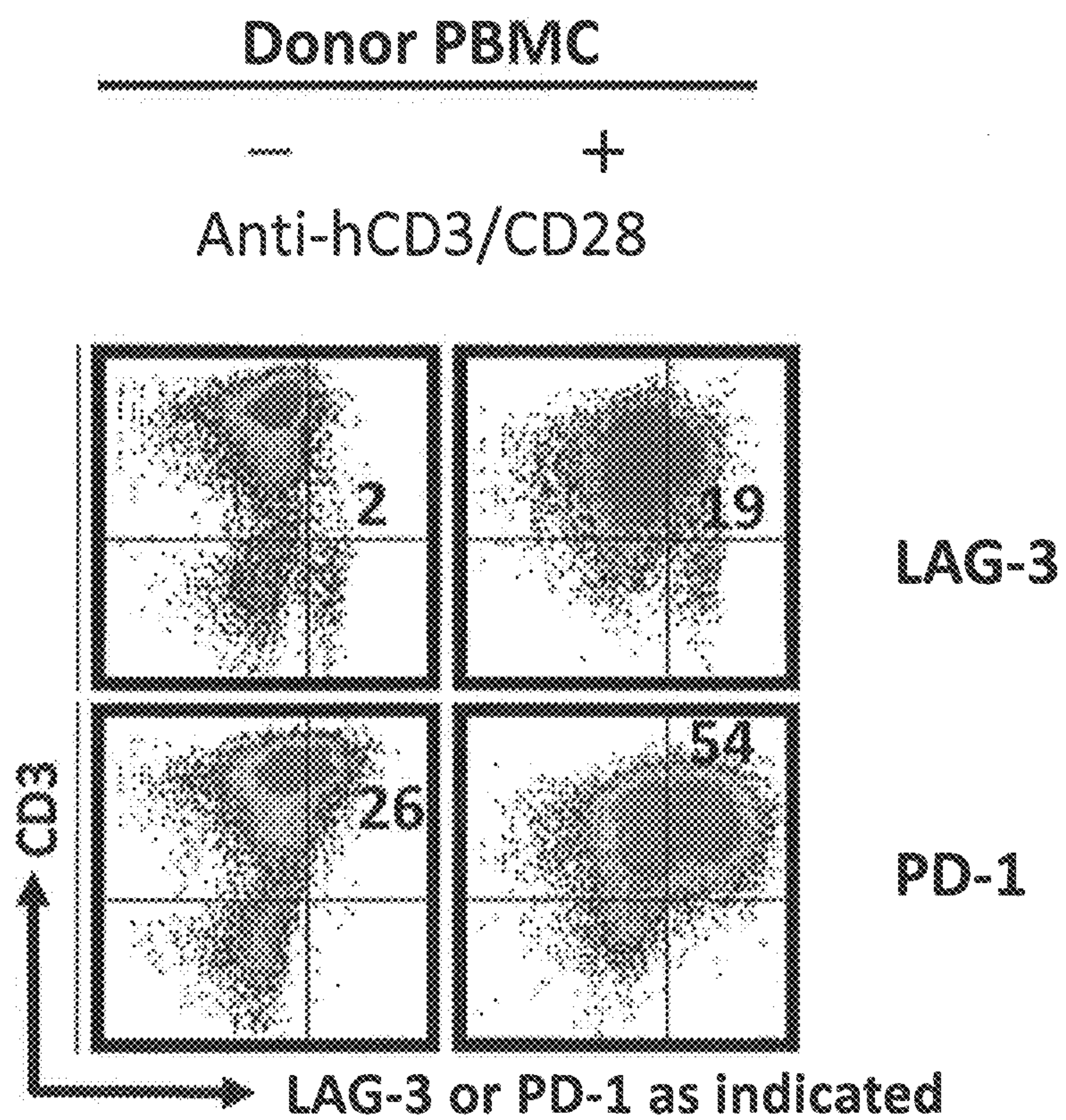


FIG. 26

Anti-LAG-3 mAb 2L2A.1 induces more IFN- γ production than a benchmark (BM) anti-LAG-3 mAb

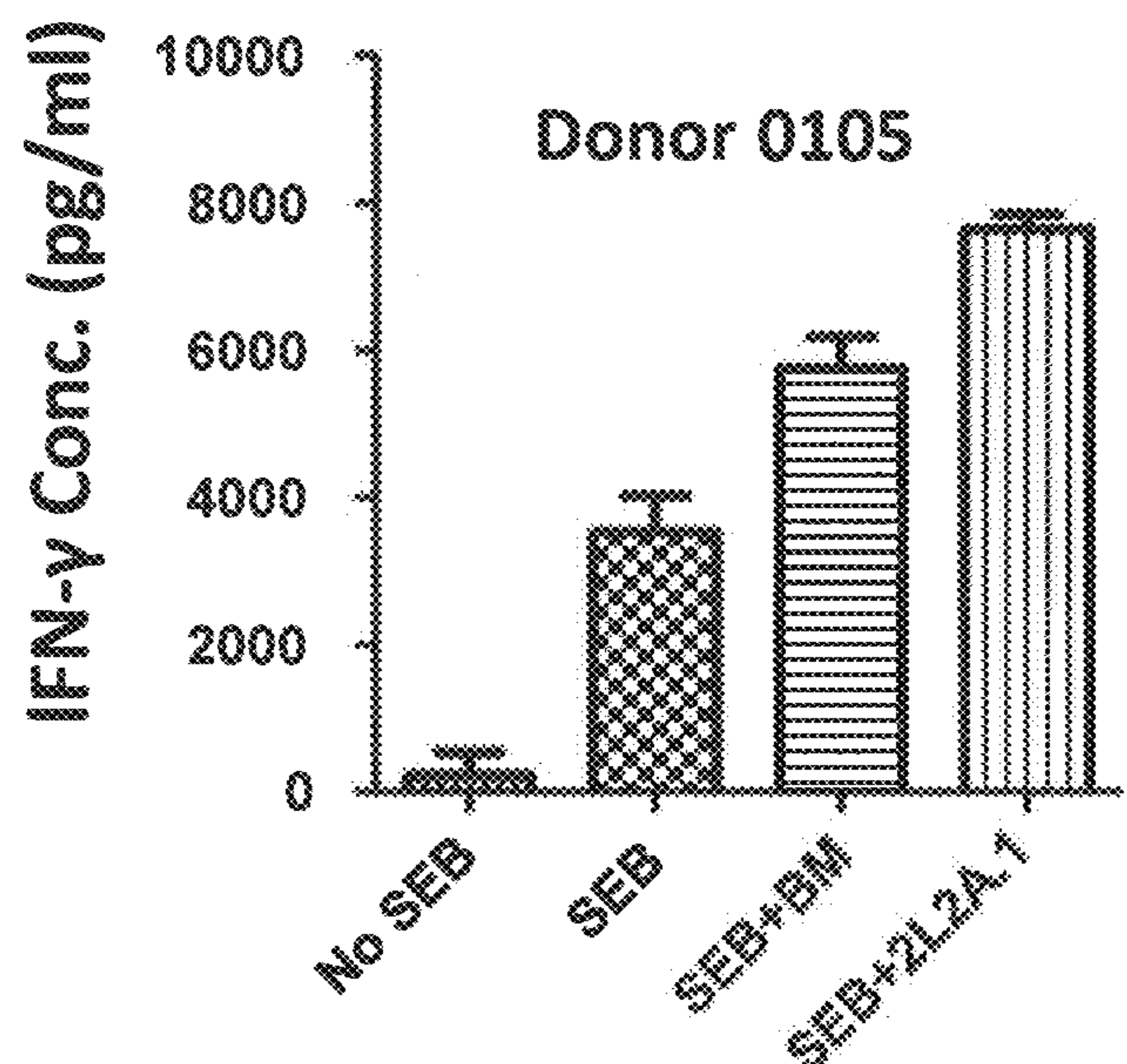


FIG. 27A

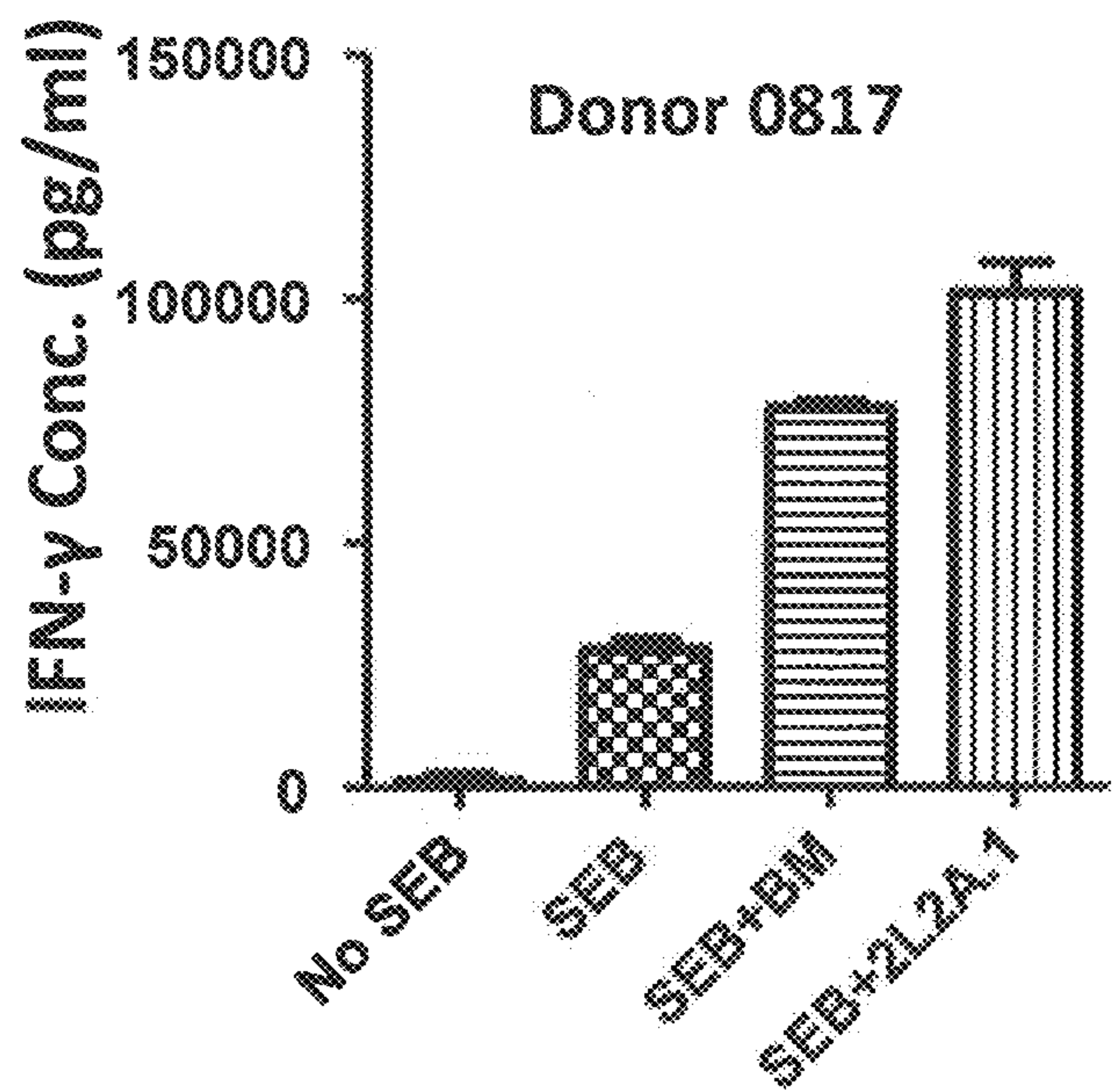


FIG. 27B

Anti-LAG-3 mAb 2L2A.1 can induce more IFN- γ production than a benchmark (BM) anti-LAG-3 mAb

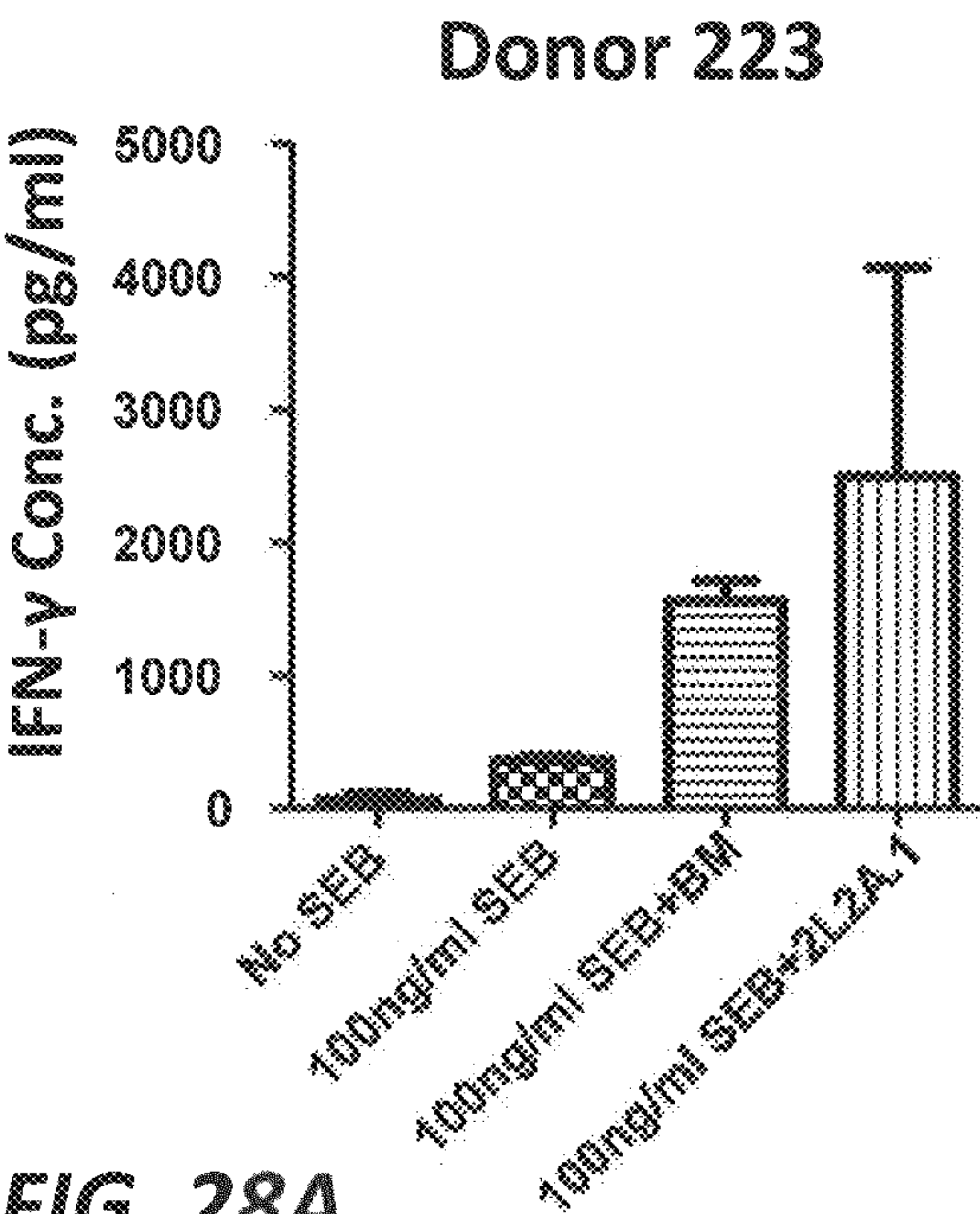


FIG. 28A

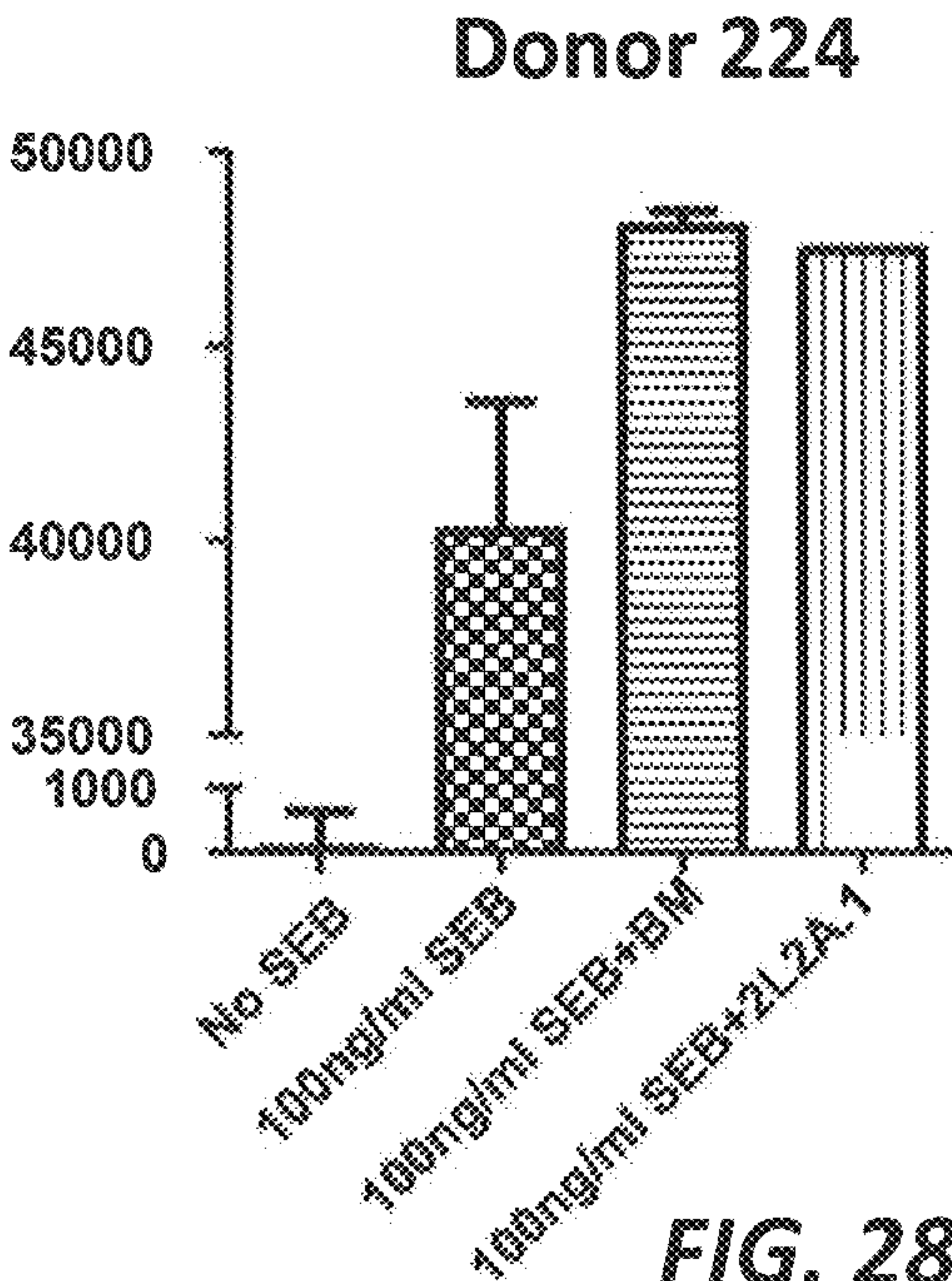


FIG. 28B

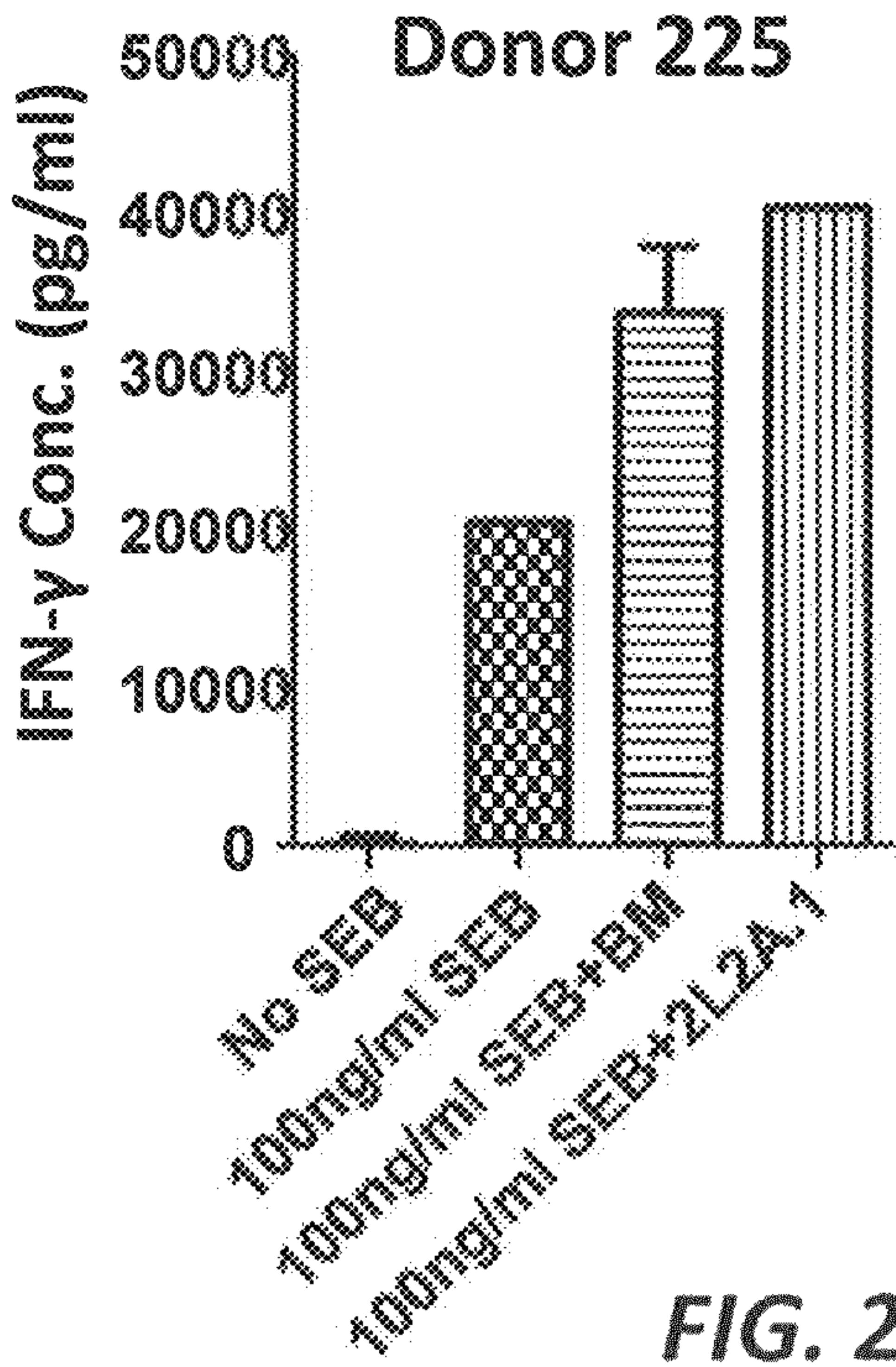


FIG. 28C

Anti-LAG-3 mAb 2L2A.1 can induce more primary T cell proliferation than a benchmark (BM) anti-LAG-3 mAb

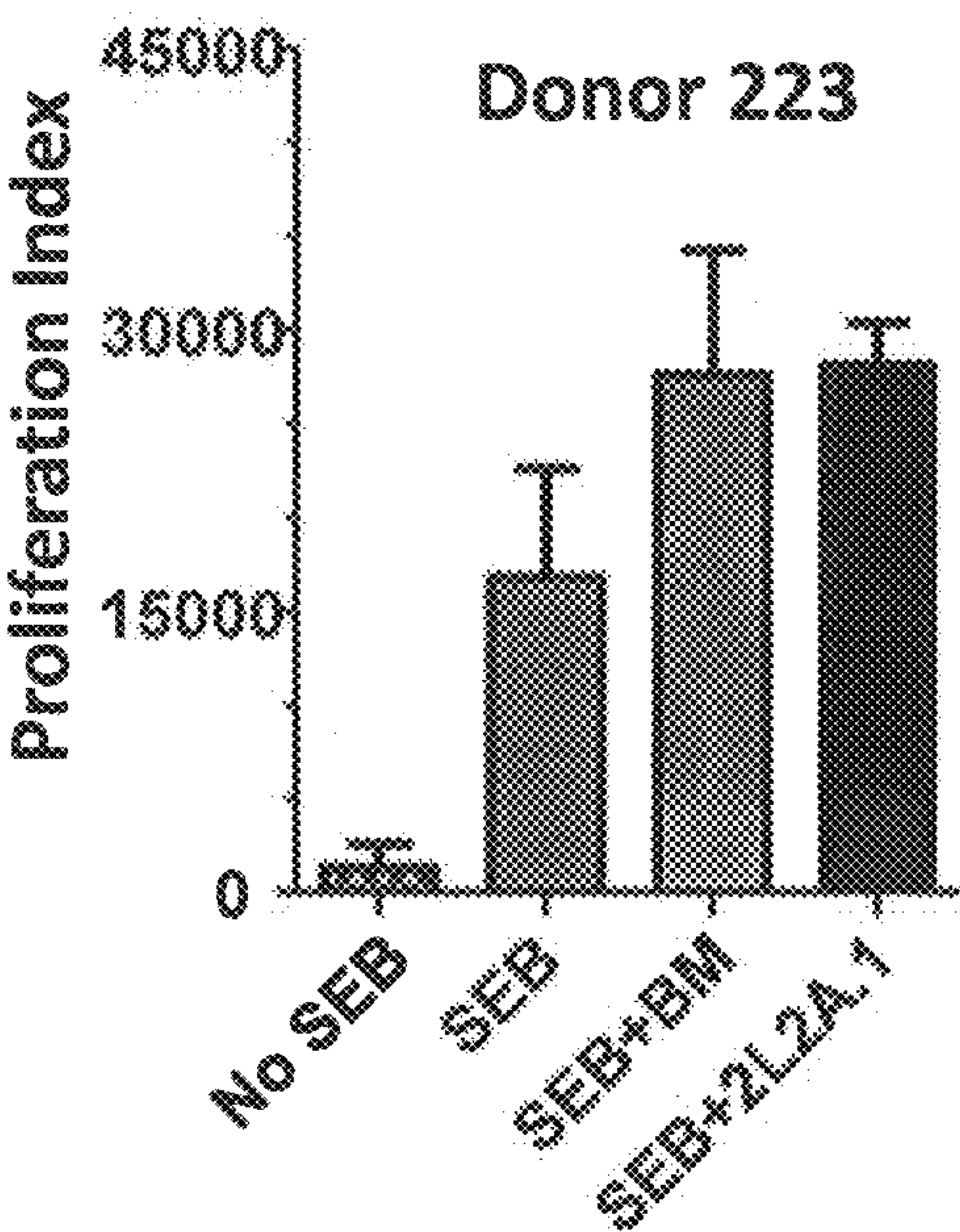


FIG. 29A

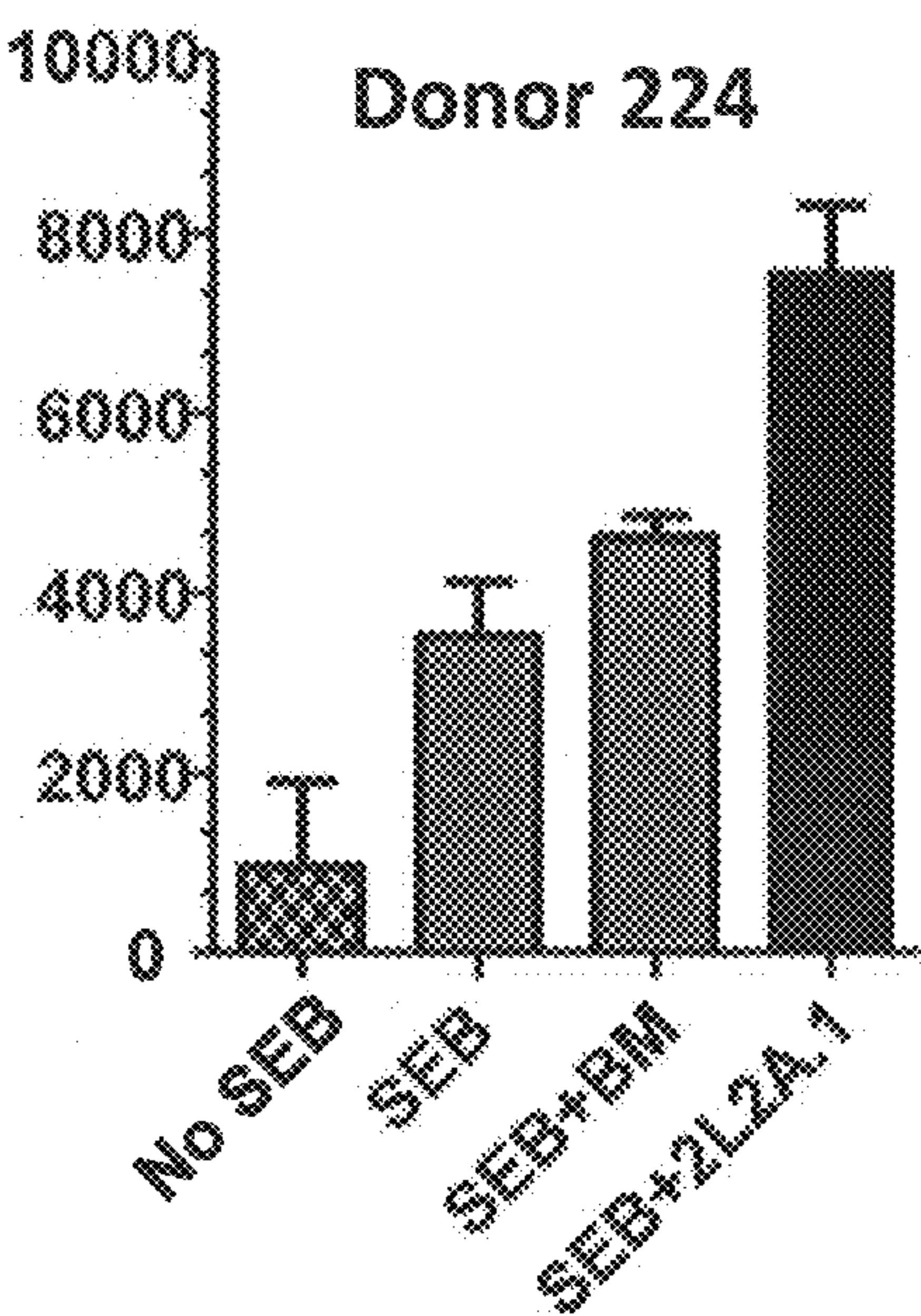


FIG. 29B

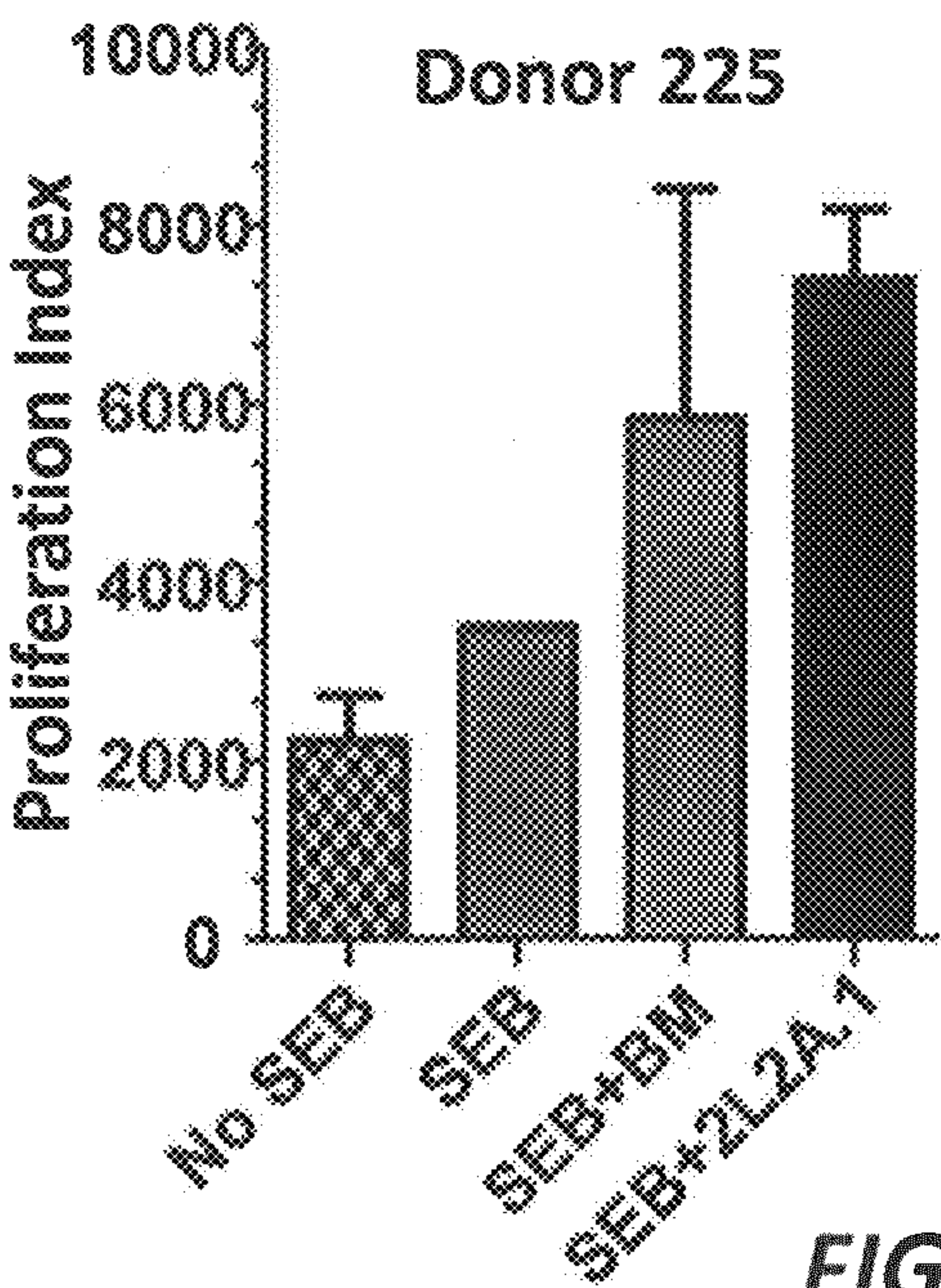


FIG. 29C

Anti-LAG-3 antibodies with TIGIT scfv

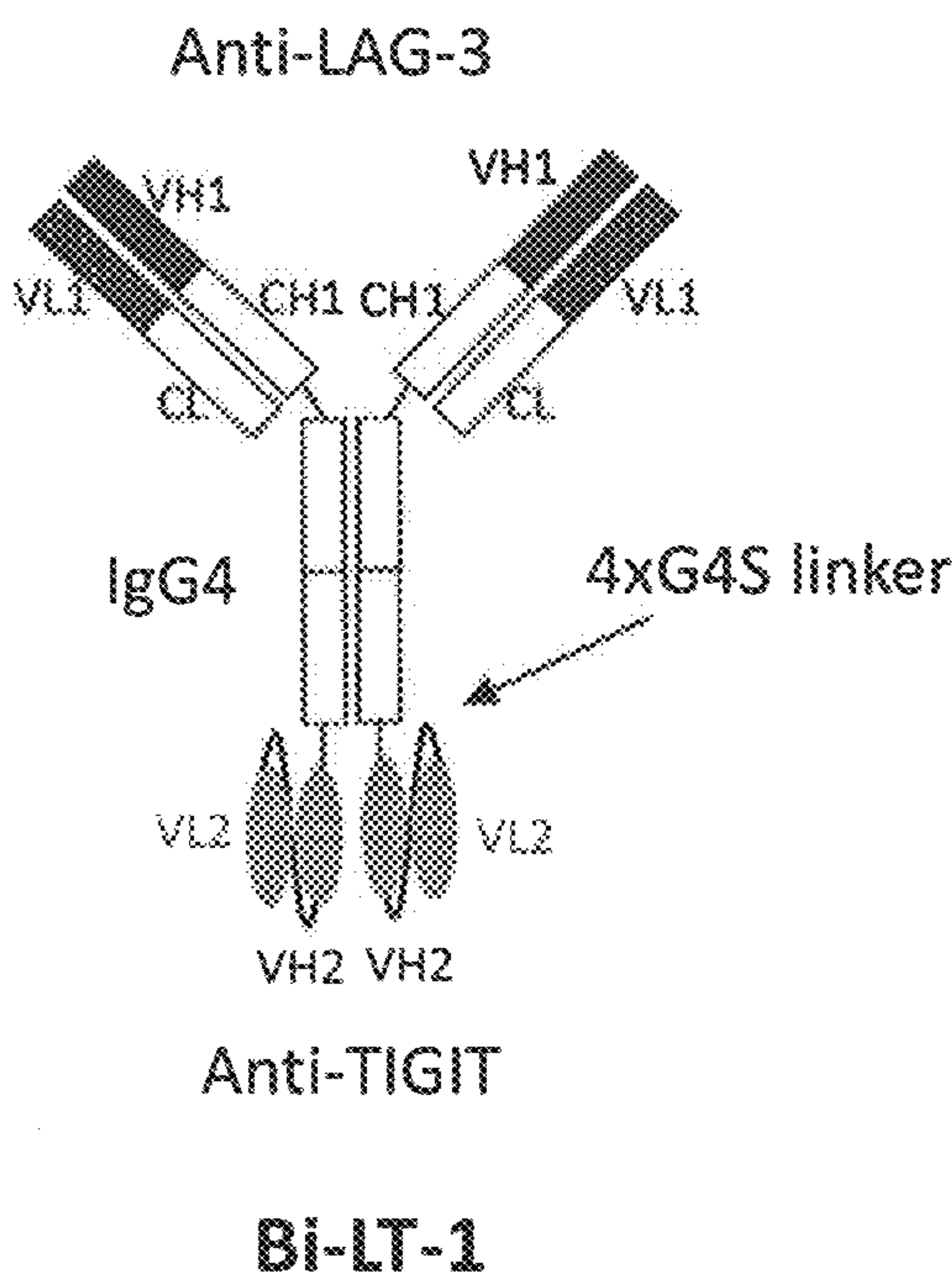


FIG. 30A

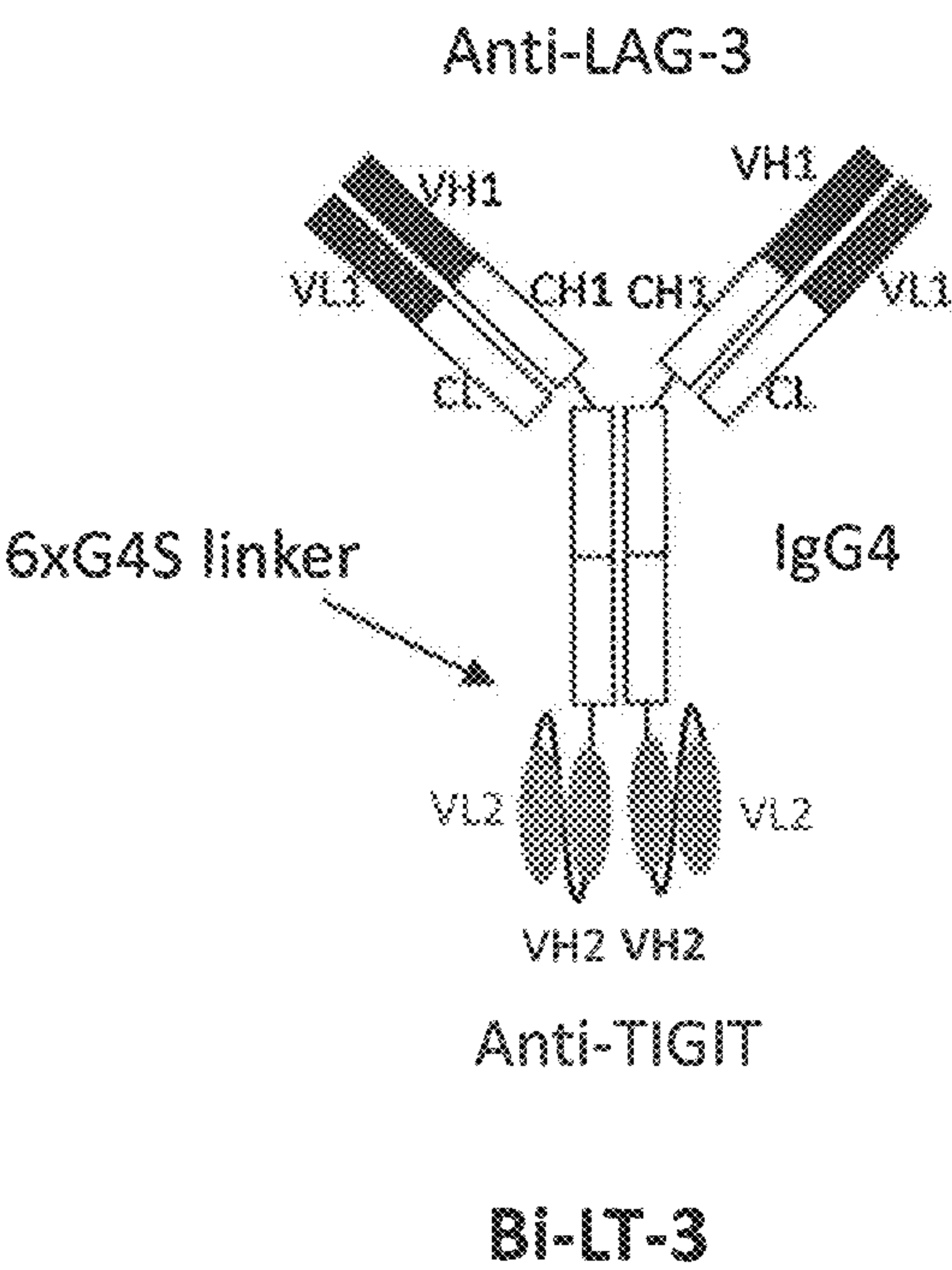


FIG. 30B

Functional Domain Sequences in FIGs. 30A-30B

VH/VL or Fusion Protein Domain	Amino Acid Sequences of Functional Domains
Anti-LAG-3 HCVR (2L2A.1)	QVQLVQSGAEVKKPGASVKVSCKASGYTLTDYYMNWMRQAPGQGLEWMGVINPYNGDT SYNQKFKGRVTMTRDTSTSTVYMESSLRSED TAVYYCVRDDGYVHYFDYWGQGTLTVSS (SEQ ID NO: 180)
Anti-LAG-3 LCVR (2L2A.1)	DIQMTQSPSSLSASVGDRVTITCRASQDISSRLTWLQQEPEKAPKRLIYATSSLD SGVPKRFSGS GSGTDFTLTISSLQPEDFATYYCLQYASSPLTFGGG TKVEIK (SEQ ID NO: 181)
Anti-TIGIT HCVR (B21-35)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGLEWMGIINPSGGRTSY AQMFQGRVTMTRDTSTSTVYMESSLRSED TAVYYCARDREEQWPVG GFDYWGQGTLTV SS (SEQ ID NO: 66)
Anti-TIGIT LCVR (B21-35)	DIQMTQSPSSLSASVGDRVTITCRASQSIRRYLNWYQQKPGKAPKLLIYSASN LQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQSYIIPPTFGQG TKVEIK (SEQ ID NO: 67)
IgG4 CHI-CH2-CH3 (hinge stabilized S231P)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK (SEQ ID NO: 155)
4xG4S linker	GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 189)
6xG4S linker	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 191)

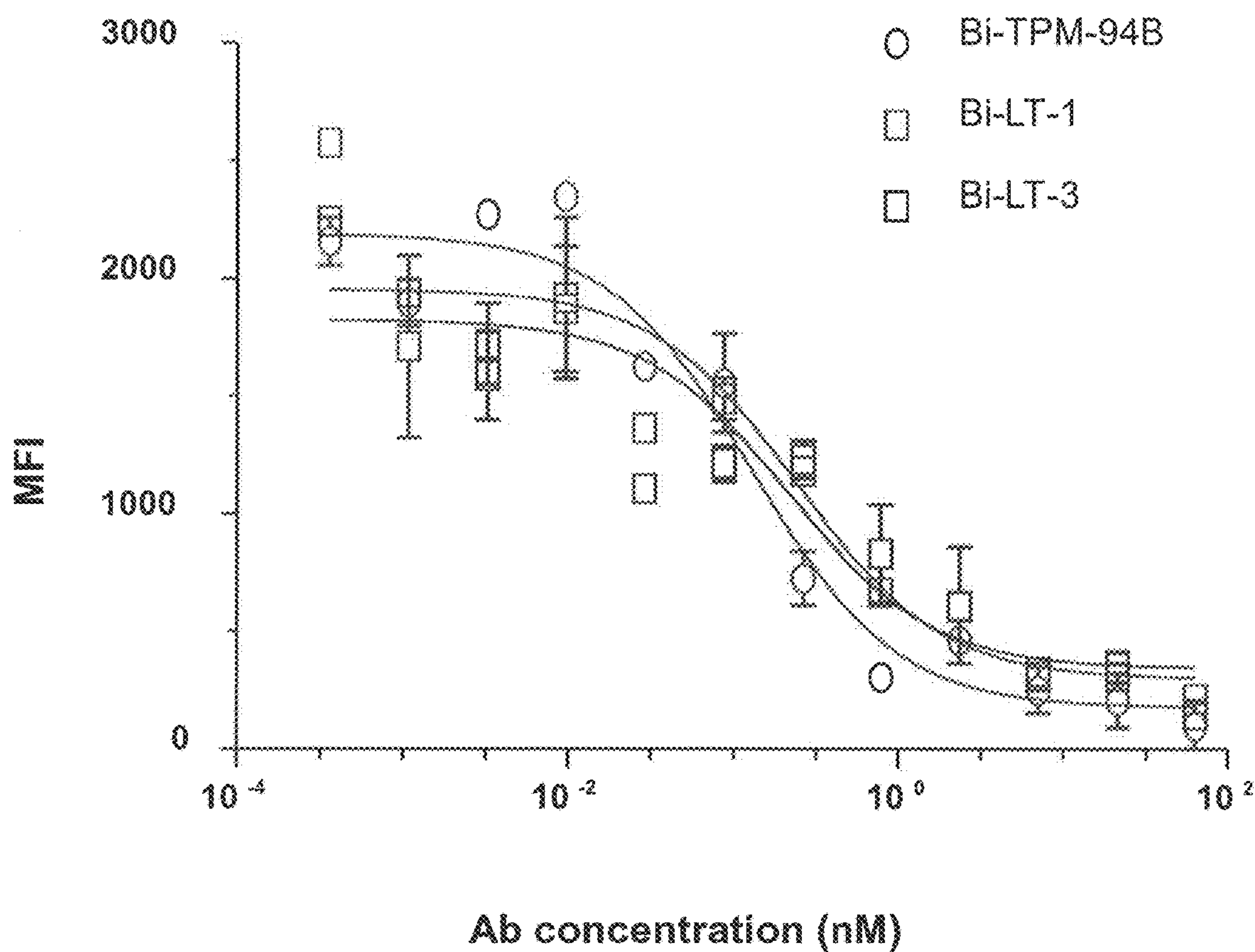
FIG. 31

HC and LC Sequences of Antagonists of Bi-LT-1 and Bi-LT-3 in FIGs. 30A-30B

Antagonist (HC/LC)	Amino Acid Sequence
Bi-LT-1 HC	QVQLVQSGAEVKKPGASVKVSCKASGYTLTDYYMNWMRQAPGQGLEWMGVINPYNGDT SYNQKFKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCVRDDGYVHYFDYWGGGTLTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHLEAHN HYTQKSLSLGKGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVR QAPGQGLEWMGIINPSGGRTSYAQMFGGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARD REEQWPVGGFYDWGGGTLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVG DRVITCRASQSIRRYLNWYQKPKAPKLLIYSASNLSGVPSRFSGSGSGTDFTLTISLQPE DFATYYCQQSYIIPPTFGQGTKVEIK (SEQ ID NO:192)
Bi-LT-1 LC	DIQMTQSPSSLSASVGDRVITCRASQDISRLTWLQQKPEKAPKRLIYATSSLD SGVPSRFSGS GSGTDFTLTISLQPEDFATYYCLQYASSPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYA CEVTHQGLSPVTKSFNRGEC (SEQ ID NO:194)
Bi-LT-3 HC	QVQLVQSGAEVKKPGASVKVSCKASGYTLTDYYMNWMRQAPGQGLEWMGVINPYNGDT SYNQKFKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCVRDDGYVHYFDYWGGGTLTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHLEAHN HYTQKSLSLGKGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVR QAPGQGLEWMGIINPSGGRTSYAQMFGGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARD REEQWPVGGFYDWGGGTLTVSSGGGGSGGGGSGGGGSGGGGSGGGGSDIQM TQSPSSLSASVGDRVITCRASQSIRRYLNWYQKPKAPKLLIYSASNLSGVPSRFSGSGSG TDFTLTISLQPEDFATYYCQQSYIIPPTFGQGTKVEIK (SEQ ID NO:193)
Bi-LT-3 LC	DIQMTQSPSSLSASVGDRVITCRASQDISRLTWLQQKPEKAPKRLIYATSSLD SGVPSRFSGS GSGTDFTLTISLQPEDFATYYCLQYASSPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYA CEVTHQGLSPVTKSFNRGEC (SEQ ID NO:194)

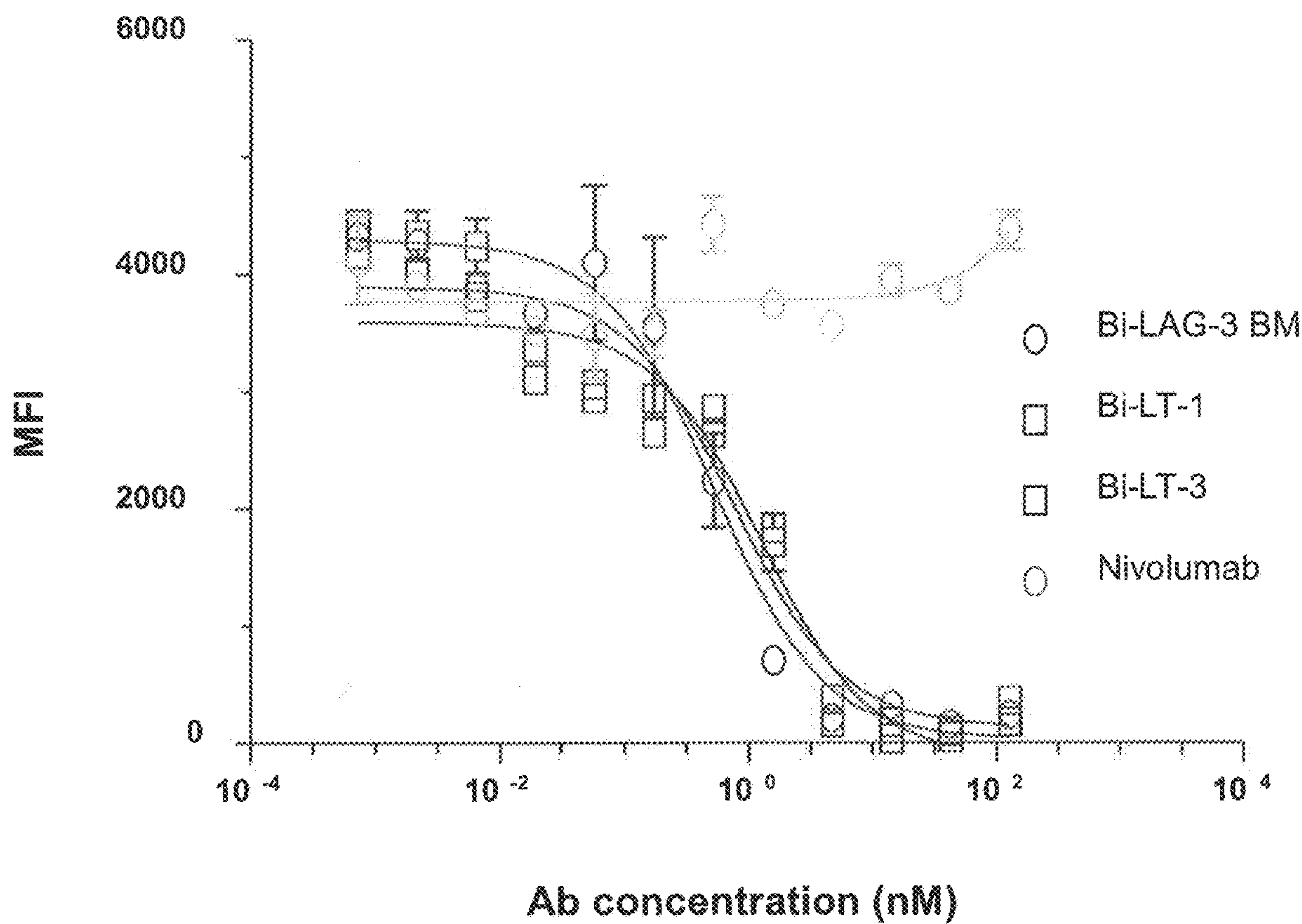
FIG. 32

Improved TIGIT scFvs with the extended 4xG4S or 6xG4S linkers fused to anti-LAG3 antibody retain bioactivity for both TIGIT and LAG3



TIGIT	IC50 (nM)
Bi-TPM-94B	0.13
Bi-LT-1	0.24
Bi-LT-3	0.22

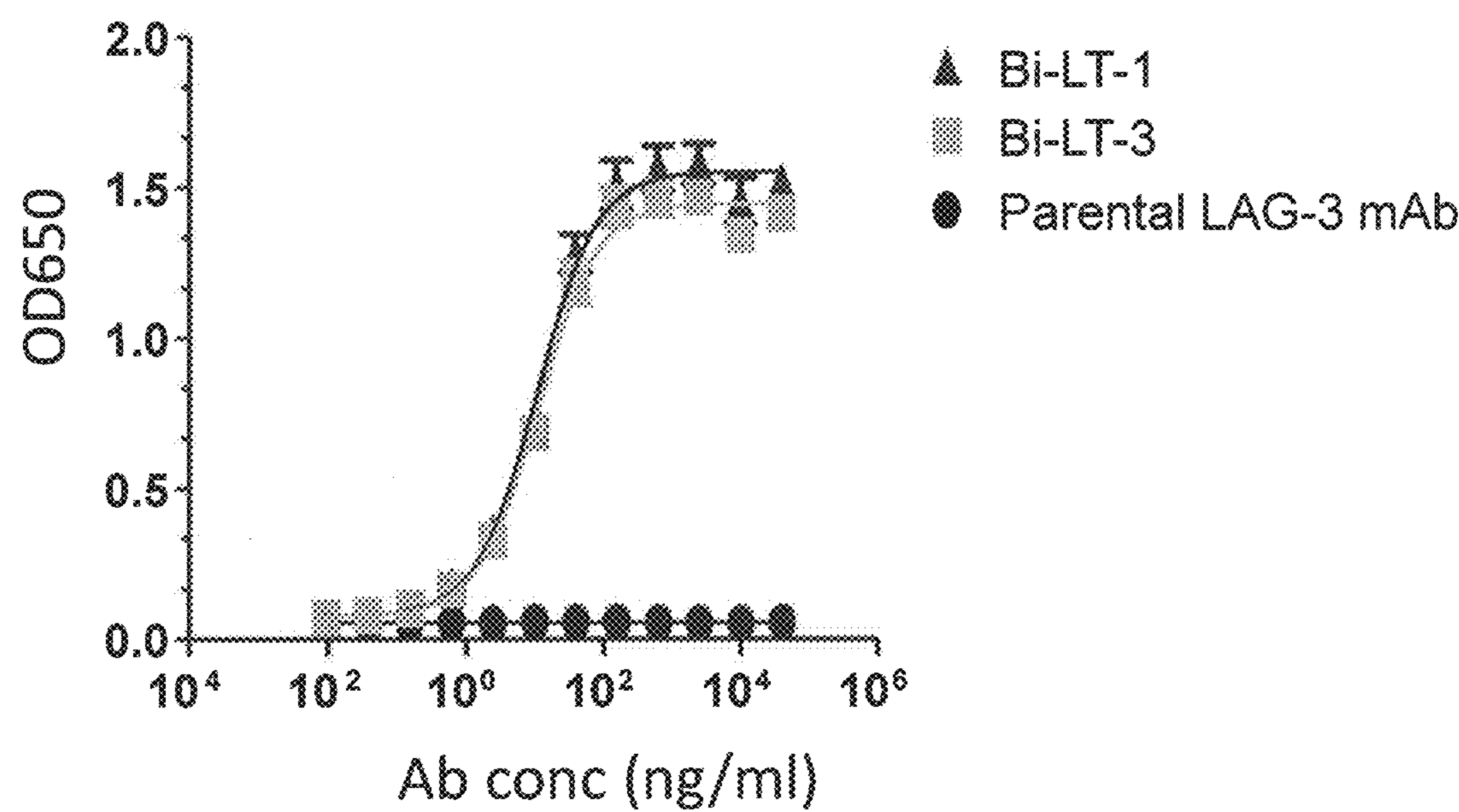
FIG. 33A



LAG-3	IC50 (nM)
Anti-LAG-3 BM	0.6
Bi-LT-1	0.7
Bi-LT-3	0.9

FIG. 33B

Bi-LT-1 and Bi-LT-3 can simultaneously bind
LAG-3 and TIGIT



Antibody	Bottom	Top	EC50 (ng/ml)
LAG-3 mAb	0.06	0.06	NA
Bi-LT-1	0.08	1.55	10.67
Bi-LT-3	0.08	1.45	10.75

FIG. 34

Improved TIGIT scfvs fused to LAG-3 antibody have good pharmacokinetic properties, similar to unfused LAG3 antibody

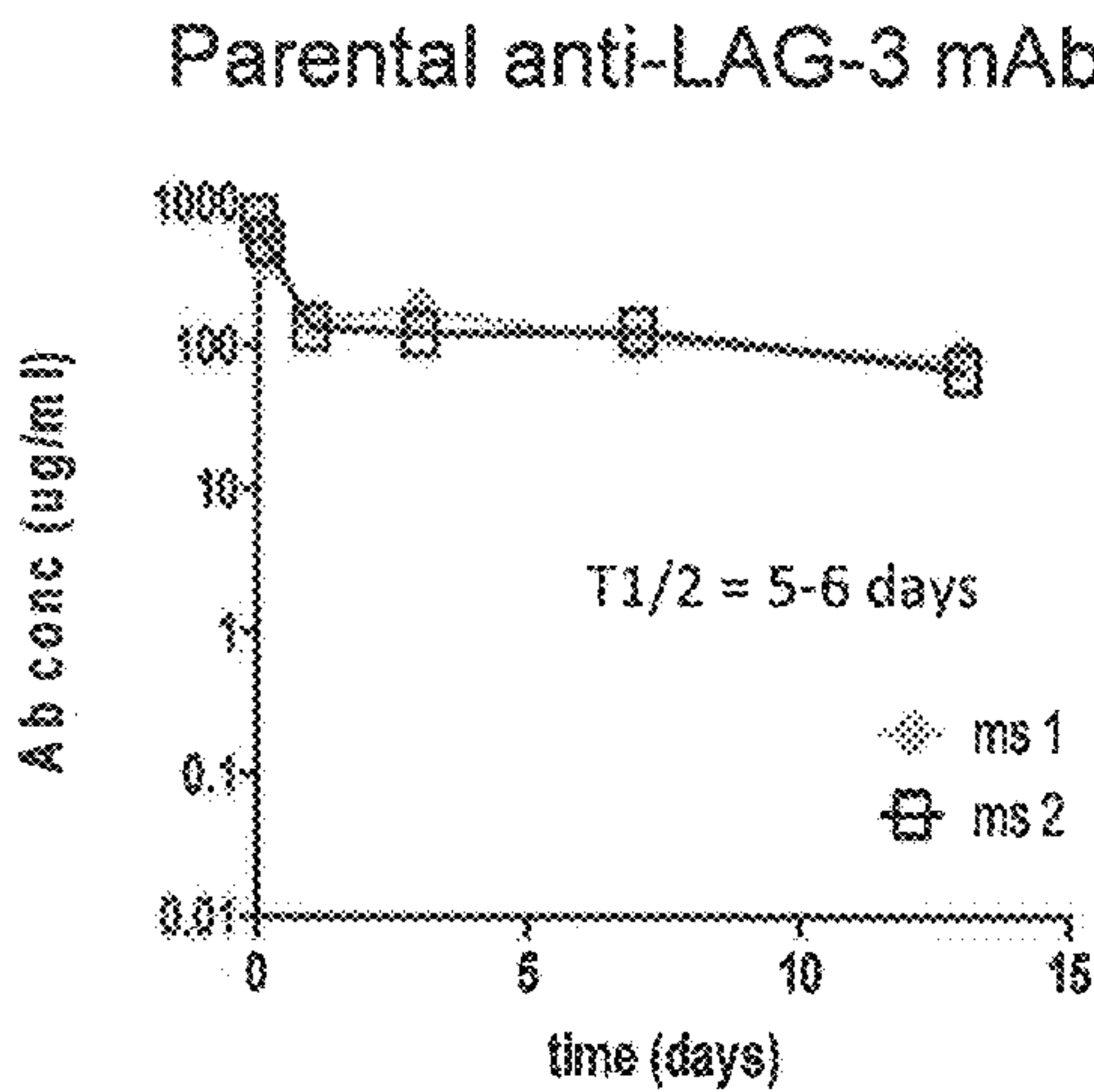


FIG. 35A

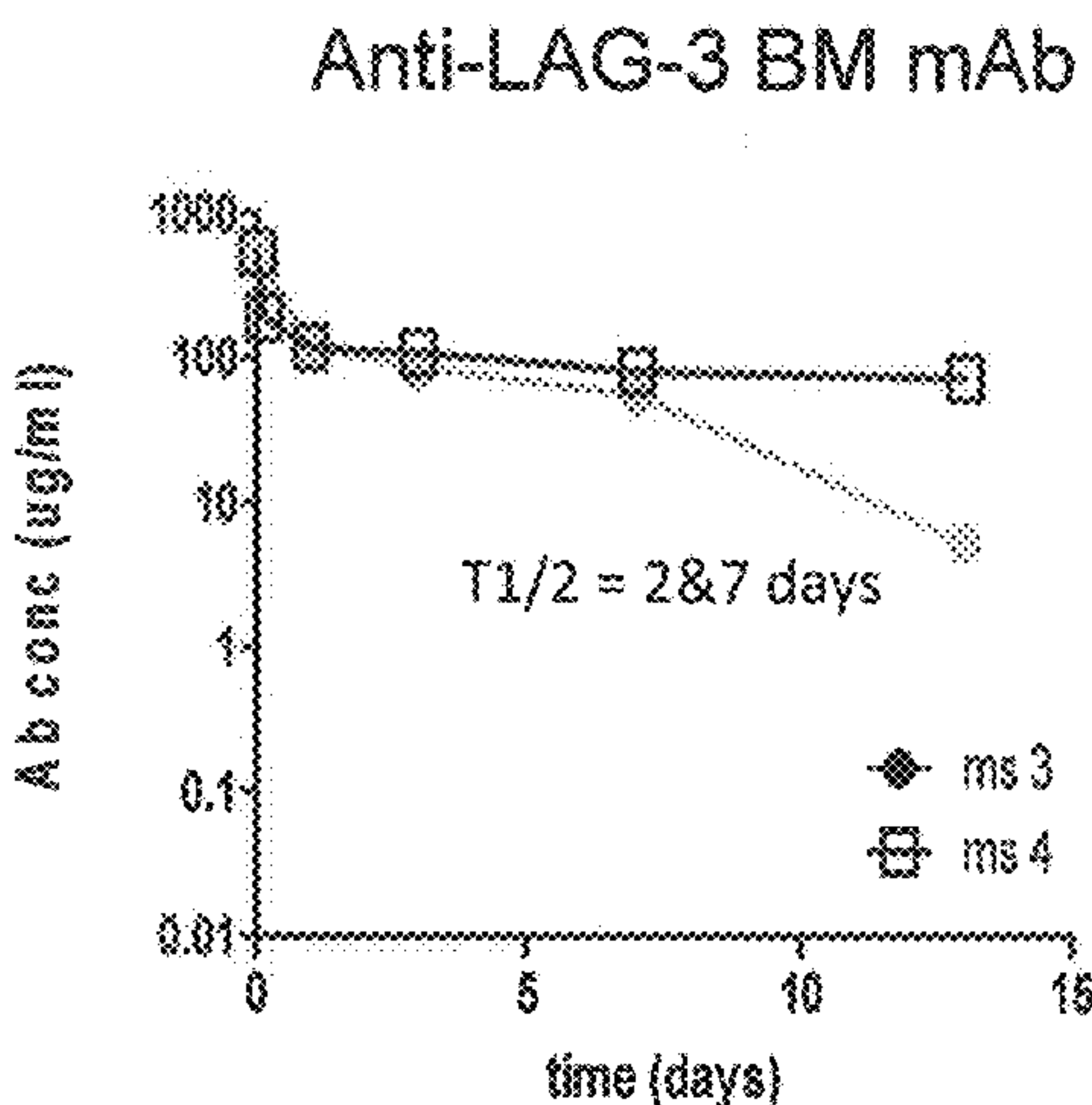


FIG. 35B

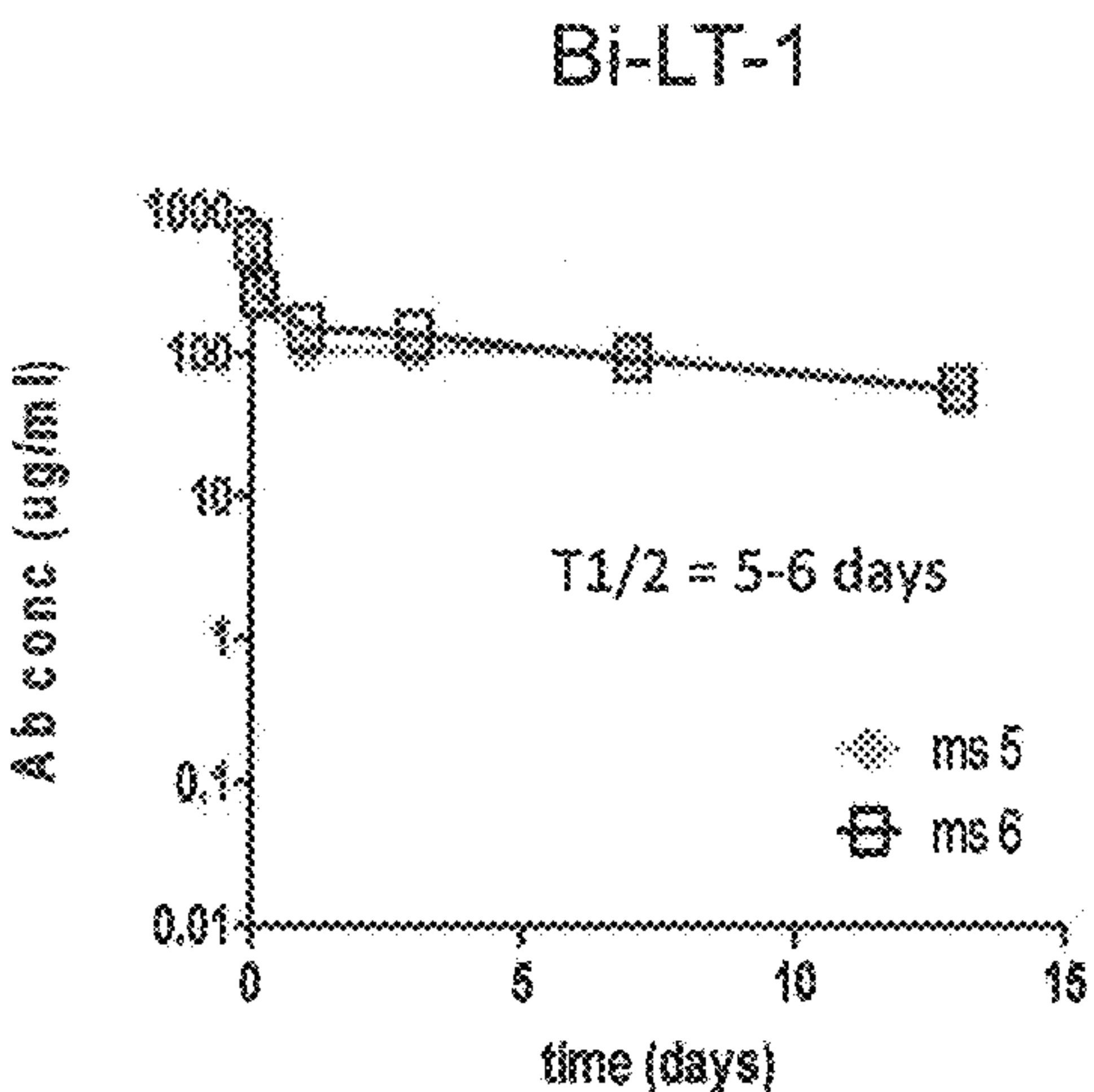


FIG. 35C

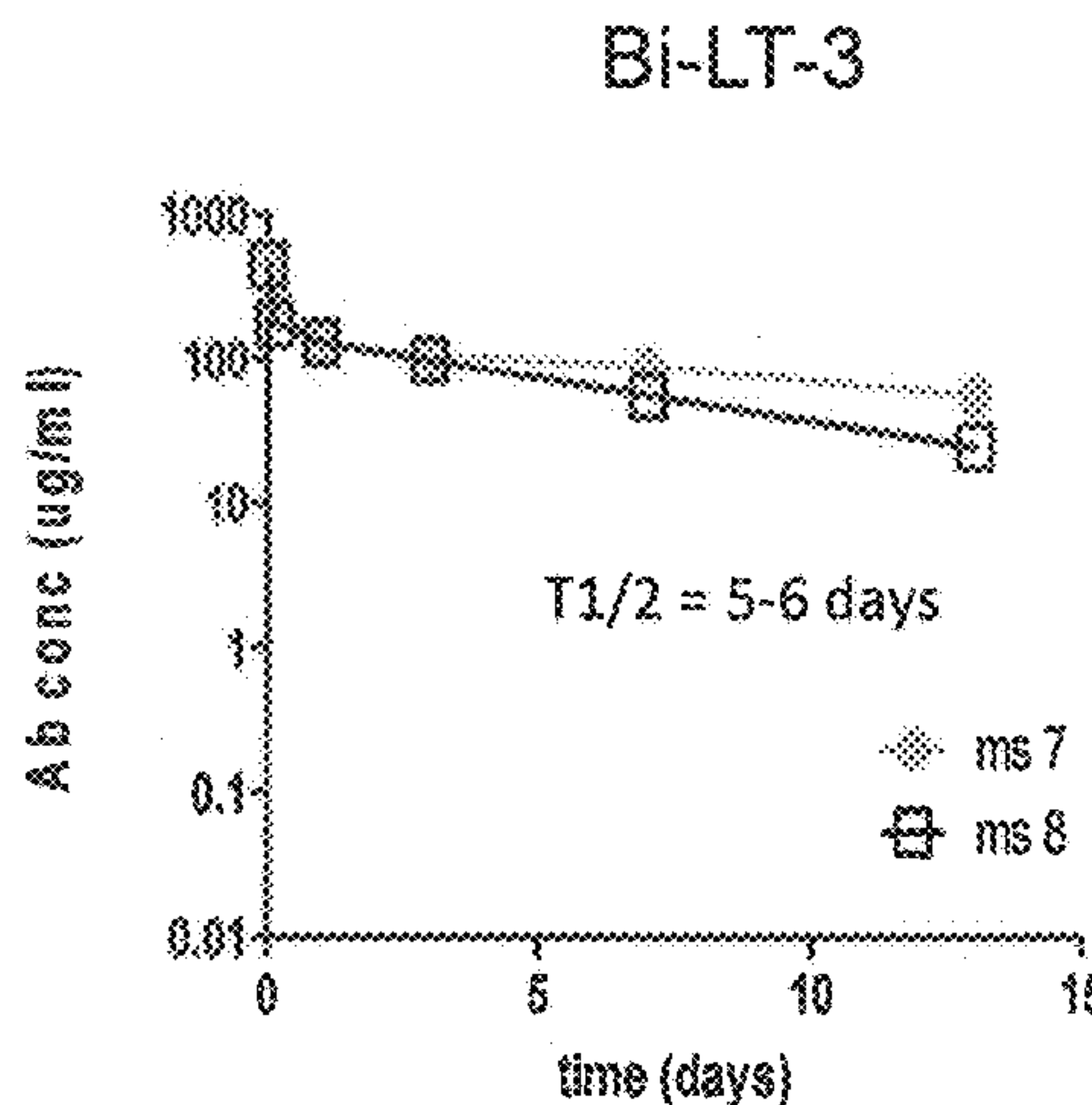


FIG. 35D

Bi-LT-1 and Bi-LT-3 with the improved TIGIT scFvs are homogenous and has good stability at 4° C for 7 days

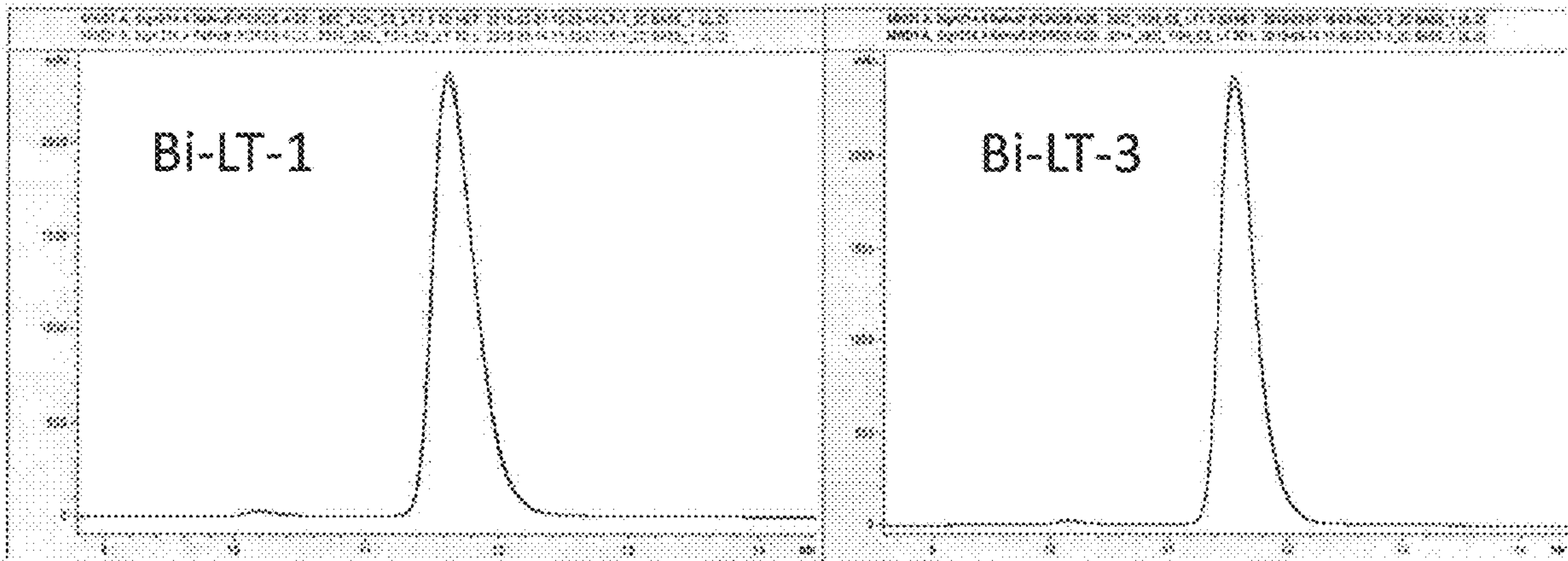


FIG. 36A

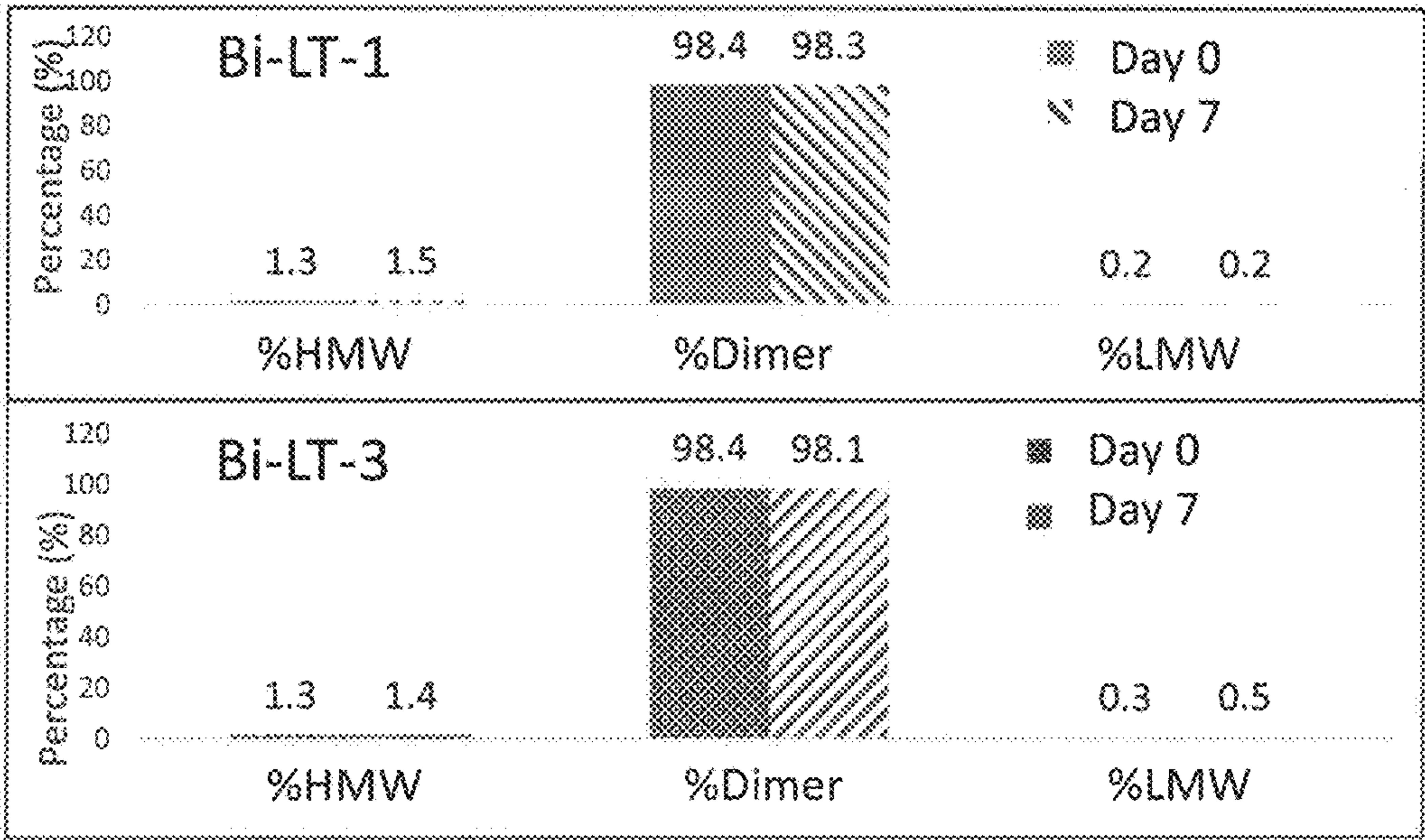


FIG. 36B

Bi-LT-1 and Bi-LT-3 are more potent than the combination of parental TIGIT and LAG-3 antibodies, since they induce more IFN- γ in a SEB stimulated PBMC assay

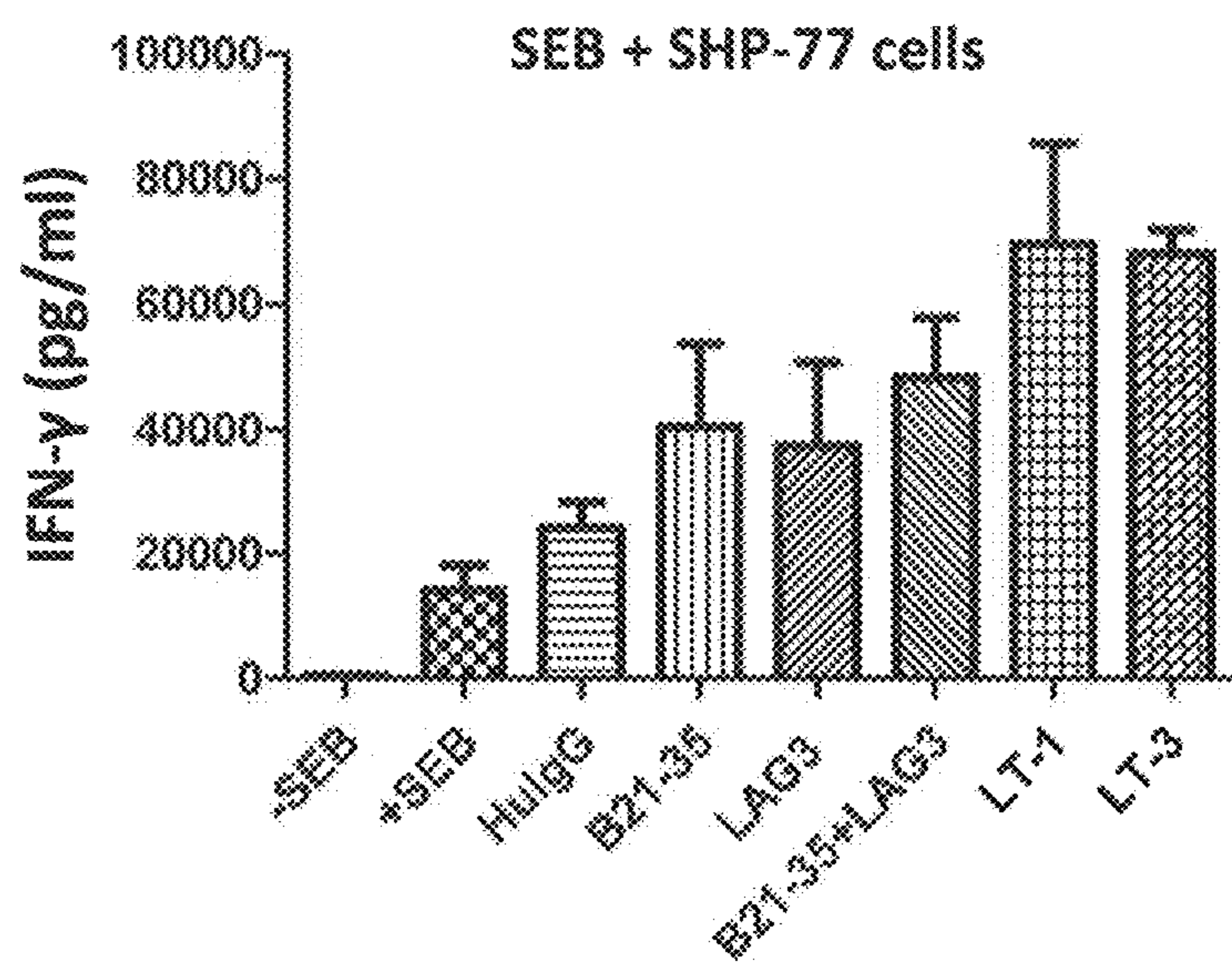


FIG. 37A

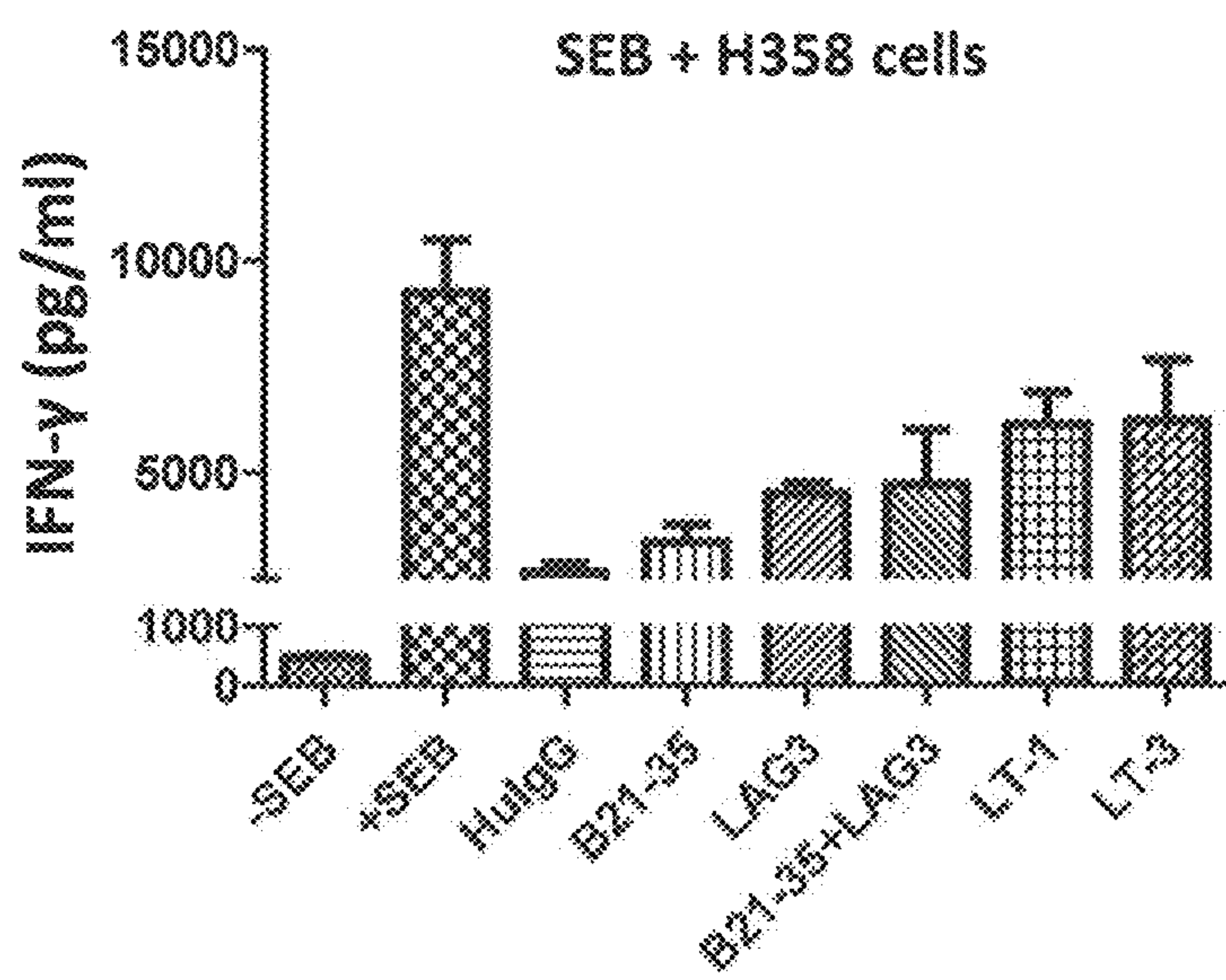


FIG. 37B

Bi-LT-1 and Bi-LT-3 are more potent than the combination of parental TIGIT and LAG-3 antibodies for the induction of T cell proliferation of SEB stimulated PBMCs

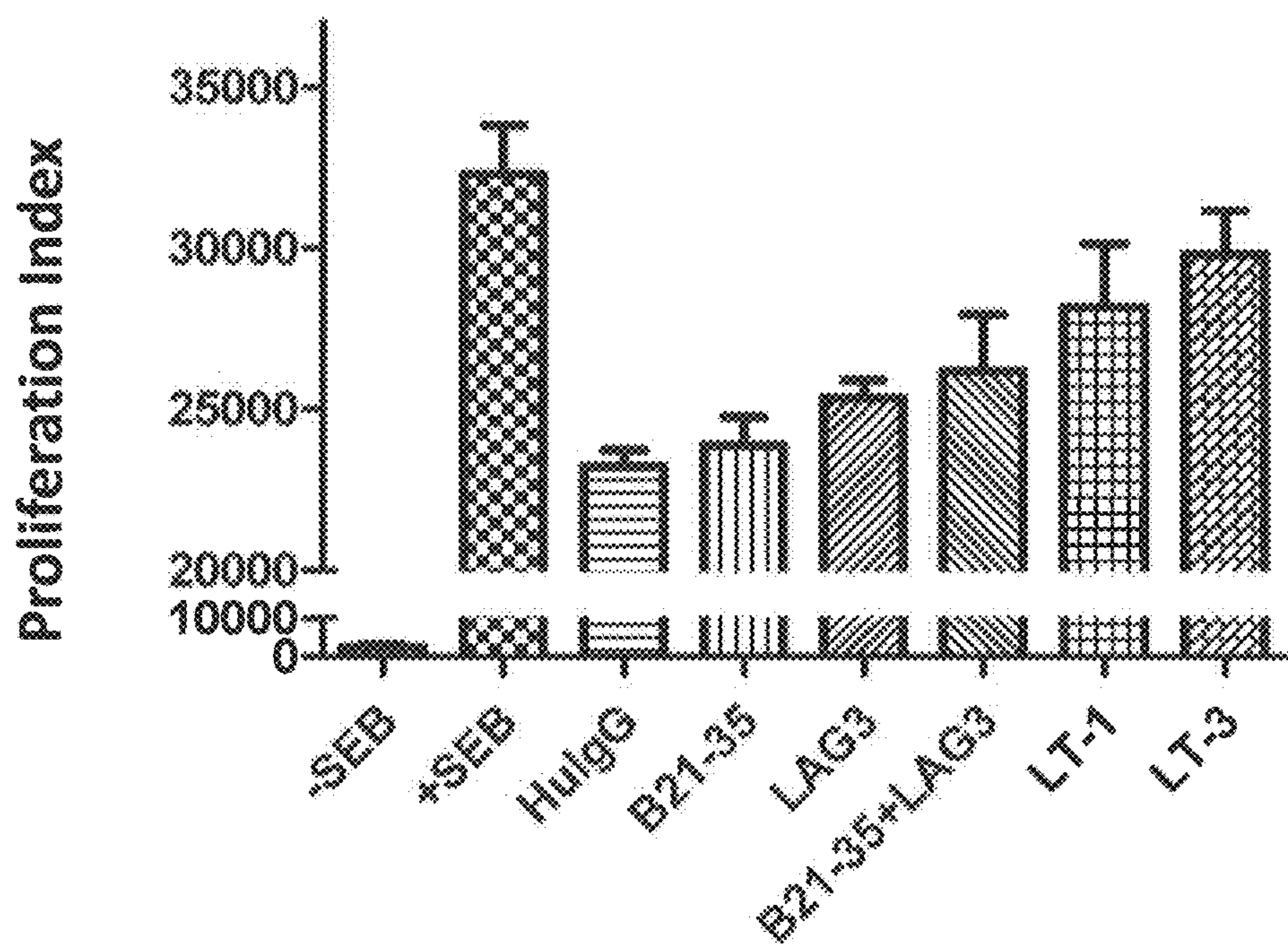


FIG. 38

SEQ ID NO	Sequence	Description/Notes
216	QVQLQESGPGGLVKPSQTLSTCTVSGYSIT	T-01 HFR1
217	WIRQPPGKGLEWIG	T-01, 02, 06, 07 HFR2
218	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	T-01, 06 HFR3
219	WGQGTSTVTVSS	T-01 HFR4
220	DIQMTQSPSSLSASVGDRVTITC	T-01, 03, 04, 05, 06, 07, 10 LFR1
221	WHQOKPGKAPKLLIY	T-01 LFR2
222	GVPSRFSGSGSGTDFLTITSSLOPEDFATYYCQOYSTP	T-01, 02 LFR3
223	FGGGTKLEIKR	T-01, 06 LFR4
224	QVKLQESGPGGLVKPSQTLSTCTVTGYSIT	T-02 HFR1
225	RVTISVDTSKNQFSLKLSSVTAADTAVYSCAR	T-02 HFR3
226	WGQGTSLTVSA	T-02, 06, 07 HFR4
227	DIQMTQSPSSLSASVGDRVTIPC	T-02 LFR1
228	WYQOKPGKAPKLLIY	T-02, 03, 04, 05, 06, 07, 10 LFR2
229	FGEGTKLEIK	T-02 LFR4
230	EVQLVOSGAEVKKPGATVKISCKVSGYTFT	T-03, 04 HFR1
231	WVQQAPGKGLEWMG	T-03, 04, 05 HFR2
232	RVTITADTSTDATYMESSLRSEDATVYYCAT	T-03, 04 HFR3
233	WGQGTSLTVSVA	T-03 HFR4
234	GVPSRFSGSGSGTDFLTITSSLOPEDFATYYC	T-03, 05, 06, 10 LFR3
235	FGAGTKLELK	T-03, 05 LFR4
236	WGQGTSLTVTVSS	T-04, 05, 08, 09, 10 HFR4
237	GVPSRFSGSGSGTDFLTITSSLOPEDATYYC	T-04 LFR3
238	FGAGTKLEIK	T-04 LFR4
239	EVQLKQSGAEVKKPGATVKISCKVSGYTFT	T-05 HFR1
240	RVTITADTSTDATYMESSLRSEDATVYFCAR	T-05 HFR3
241	QVQLQESGPGGLVKPSQTLSTCTVSGGSVS	T-06 HFR1
242	EVQLQESGPGGLVKPSQTLSTCAVSGYSIT	T-07 HFR1
243	RVTMSVDTSKNQFSLKLSSVTAADTAVYYCTR	T-07 HFR3
244	GAPSRFSGSGSGTDFLTITSSLOPEDFGIYYC	T-07 LFR3
245	FGGGTKLEFK	T-07 LFR4
246	QVQLVQSGSELKKPGASVKVSKASGYTFT	T-08 HFR1
247	WVRQAPGQGLEWMG	T-08, 10 HFR2
248	RFVFSLDTSVSTAYLQISLKAEDTAVYYCAR	T-08 HFR3
249	DVVMTQSPSLPVTLGQPASISC	T-08 LFR1
250	WFQQRPGQSPRVLIY	T-08 LFR2
251	GVPDRFSGSGSGTDFLTISKISVEAEDVGYYC	T-08 LFR3
252	FGRGTKLEIK	T-08 LFR4
253	QVTLKESGPTLVKPTQTLTLCTFSGFSL	T-09 HFR1
254	WIRQPPGKALEWLA	T-09 HFR2
255	RLTITKDTSKNQVVLTMNMDPVDATYYCAR	T-09 HFR3
256	QAVVTQEPSTVSPGGTVTLTC	T-09 LFR1
257	WVQOKPGQLFRGLIG	T-09 LFR2
258	WVPARFSGSLIGDKAALTLSGVQPEDEAEYFC	T-09 LFR3
259	FGGGTKLTVL	T-09 LFR4
260	QVQLVQSGAEVKKPGASVKVSKASGYTFT	T-10 HFR1
261	RVTMTTRDTSTSTVYMESSLRSEDATVYYCAR	T-10 HFR3
262	FGQGTKVEIK	T-10 LFR4

FIG. 39A

SEQ ID NO	Sequence	Description/Notes
263	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	PD-01 HFR1
264	WVRQAPGKGLEWVS	PD-01 HFR2
265	RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAK	PD-01 HFR3
266	WGQGTSVTVSS	PD-01 HFR4
267	DIQMTQSPSSVSASVGDRVITC	PD-01 LFR1
268	WYQQKPGKAPKLLIY	PD-01, 02, 03, 04; PL-02, 03 LFR2
269	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC	PD-01, 02, 03, 04 LFR3
270	FGGGTKLEIK	PD-01; PL-05 LFR4
271	QVQLVQSGAEVKKPGASVKVSCKASDYTFT	PD-02, 03, 04 HFR1
272	WLRQAPGQGLEWMG	PD-02 HFR2
273	RTTSTRDTSISTAYMELSRSDDTVYYCTR	PD-02 HFR3
274	WGQGTLLTVSS	PD-02, 04, 05, 06; PL-01, 02, 03, 04, 06, 07, 08 HFR4
275	DIQMTQSPSSLSASVGDRVITFC	PD-02, 04 LFR1
276	FGGGTKVEIK	PD-02, 04, 05; PL-01, 04, 06, 07, 08 LFR4
277	WVRQAPGQGLEWMG	PD-03, 04, 05, 06; PL-02, 03, 04, 08 HFR2
278	RVTSTRDTSISTAYMELSRSDDTVYYCA	PD-03, 04; PL-01 HFR3
279	WGQGTLLTVSS	PD-03; PL-05 HFR4
280	DIQMTQSPSSLSASVGDRVITC	PD-03 LFR1
281	FGAGTKLDLK	PD-03 LFR4
282	FGGGTKVEIK	PD-04, 05; PL-01, 04, 06, 07, 08 LFR4
283	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	PD-05, 06; PL-01, 02, 03, 04, 06, 07, 08 HFR1
284	RVTMTDRDTSISTAYMELSSLRSED TAVYYCAR	PD-05 HFR3
285	DIVLTQSPASLAVSPGQRATITC	PD-05 LFR1
286	WYQQKPGQPPKLLIY	PD-05 LFR2
287	GVPARFSGSGSGTDFTLTINPVEANDTANYYC	PD-05 LFR3
288	RVTLTADTSTSTVYMELSSLRSED TAVYYCA	PD-06 HFR3
289	DIQMTQSPSFLSASVGDRVITC	PD-06 LFR1
290	WYQQKPGKAPKALIIY	PD-06 LFR2
291	GVPSRFSGSGSGTEFTLTISLQPEDFATYYC	PD-06 LFR3
292	FGQGTKLEIK	PD-06 LFR4

FIG. 39B

SEQ ID NO	Sequence	Description/Notes
293	WMKQAPGQGLEWMG	PL-01 HFR2
294	DIQMTQSPSSLSASVGDRVTISC	PL-01, 02, 03, 04, 08 LFR1
295	WYQQKPGKAPKLLIK	PL-01, 04, 08 LFR2
296	GVPSRFSGSGSGTDFLTISLQPEDFATYFC	PL-01, 04, 08 LFR3
297	KATMTRDKSSSTVYMELSSLRSEDTAVYYCAR	PL-02 HFR3
298	GVPSRFSGSGSGTDFLTISLQPEDATYFC	PL-02, 03 LFR3
299	FGQGTKVEIK	PL-02, 03 LFR4
300	RVTMTRDTSISTAYMELSRISDDTAVYYCAR	PL-03, 08 HFR3
301	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR	PL-04 HFR3
302	DVQLQESGPGLVKPSQSLTCTVTGYSIT	PL-05 HFR1
303	WIQFPGNKLEWMG	PL-05 HFR2
304	RISITRDTSKNQFFLQNLNVTTEDTATYYCAN	PL-05 HFR3
305	DIVMTQSHKFMSTSVGDRVSITC	PL-05 LFR1
306	WYQQKPGQSPKLLIF	PL-05 LFR2
307	GVPDRFTGSGSGTDYTLTISSVQAEDLALYYC	PL-05 LFR3
308	WVRQAPGQRLWWMGW	PL-06, 07 HFR2
309	RVTITRDTASTAYMELSSLRSEDTAVYYCAR	PL-06, 07 HFR3
310	DIQMTQSPSSLSAFVGDRVTITC	PL-06 LFR1
311	WYQQKPGKAPKLLIH	PL-06 LFR2
312	GVPSRFSGSGSGRDTFTISLQPEDATYYC	PL-06 LFR3
313	EIVLTQSPVTLISLSPGERATLSC	PL-07 LFR1
314	WYLQKPGQAPRLLIK	PL-07 LFR2
315	PARFSGSGSGSDFTLTISLLEPEDFAVYYC	PL-07 LFR3
316	QVQLVQSGAEVKKPGASVKVSCKASGYTLT	2L2A.1 HFR1
317	WMRQAPGQGLEWMG	2L2A.1 HFR2
318	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCVR	2L2A.1 HFR3
319	WGQGTLLTVSS	2L2A.1, 2L2A.6, 3L1A HFR4
320	DIQMTQSPSSLSASVGDRVTITC	2L2A.1, 2L2A.6, 2L27B LFR1
321	WLQKKPEKAPKRLIY	2L2A.1 LFR2
322	GVPSRFSGSGSGTDFLTISLQPEDFATYYC	2L2A.1, 2L2A.6, 2L27B LFR3
323	FGGGTKVEIK	2L2A.1, 2L2A.6, 2L27B LFR4
324	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	2L2A.6 HFR1
325	WVRQAPGQGLEWMG	2L2A.6 HFR2
326	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR	2L2A.6 3L1A HFR3
327	WLQKKPGKAPKRLIY	2L2A.6, 3L1A LFR2
328	QVQLVQSGAEVKKPGASVKVSCKASGFTFS	2L27B HFR1
329	WVRQAPGQGLEWMGL	2L27B HFR2
330	RVTMTRDTSTSTVYMELSSLRSEDTAVYFC	2L27B HFR3
331	FDYWDDGYVVEHFDYWGGTLLTVSS	2L27B HFR4
332	WYQQKPGKAPKRLIY	2L27B LFR2
333	QVQLVQSGAEVKKPGASVKVSCKASGYTF	3L1A HFR1
334	DIQMTQSPSTLSASVGDRVTITC	3L1A LFR1
335	WLAWYQQKPGKAPKLLIY	3L1A LFR2
336	GVPSRFSGSGSGTEFTLTISLQPDDEFATYYC	3L1A LFR3
337	FGQGTKLEIK	3L1A LFR4

FIG. 39C

BISPECIFIC ANTAGONIST COMPRISING A LAG-3 BINDING DOMAIN

This application is a Continuation of U.S. patent application Ser. No. 16/457,421, filed Jun. 28, 2019, which claims priority to U.S. Provisional Patent Application Ser. No. 62/691,658, filed Jun. 29, 2018 and U.S. Provisional Patent Application Ser. No. 62/823,989, filed Mar. 26, 2019, the contents of which are expressly incorporated herein by reference herein.

FIELD

The present application relates generally to cancer treatment and, in particular, to bispecific inhibitors capable of modulating pathways associated with tumorigenesis and tumor immunity.

BACKGROUND

The inability of the host to eliminate cancer cells remains a major problem. Although an increasing number of therapeutic monoclonal antibodies have been approved for treatment of various cancers, emergence of resistance to these antibodies is frequently observed, given the many different molecular pathways underlying cancer growth and progression to metastasis. Although the immune system is the principal mechanism of cancer prevention, cancer cells counteract immunosurveillance. Natural control mechanisms have been identified that limit T-cell activation so as to prevent collateral damage resulting from unrestrained T-cell activity. This process has been exploited by tumor cells to evade immune responses. Restoring the capacity of immune effector cells, especially T cells, to recognize and eliminate cancer is a major objective in immunotherapy.

The need exists for improved therapeutic binding antagonists or antibodies and methods of treating cancer and chronic viral infections with such reagents.

SUMMARY

One aspect of the present application relates to bispecific antitumor antagonists that comprise a first targeting domain that specifically binds to an immune checkpoint regulator; a second targeting domain in the form of an scFv that specifically binds to TIGIT; and an immunoglobulin scaffold structurally linked to the first and second targeting domains, wherein the first targeting domain is positioned at N-terminal end of the antagonist, and wherein the second targeting domain is positioned at a C-terminal end of the antagonist and is linked to the immunoglobulin scaffold through a linker. In some embodiments, linker comprises 4 or 6 copies of the amino acid sequence G4S (4×G4S and 6×G4S, respectively).

In some embodiments, the first targeting domain specifically binds to PD-1, PD-L1 or LAG-3.

Another aspect of the present application relates to humanized anti-LAG-3 antibodies that inhibit binding of ligands to LAG-3.

Another aspect of the present application relates to a method for treating a cell proliferative disorder. The method comprises administering to a subject in need thereof an effective amount of a bispecific antitumor antagonist or anti-LAG-3 antibody of the present application.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows complementarity determining region (CDR) sequences of certain anti-TIGIT mAbs. The framework

region (FR) sequences flanking the anti-TIGIT CDR sequences are listed in FIG. 39A as SEQ ID NOS: 216-262.

FIGS. 2A-2C show several embodiments of anti-TIGIT antibody variable domain sequences.

FIG. 3 shows CDR sequences of certain anti-PD-1 mAbs. The FR sequences flanking the anti-PD-1 CDR sequences are listed in FIG. 39B as SEQ ID NOS: 263-292.

FIGS. 4A-4B show several embodiments of anti-PD-1 antibody variable domain sequences.

FIG. 5 shows CDR sequences of certain anti-PD-L1 mAbs. The FR sequences flanking the anti-PD-L1 CDR sequences are listed in FIG. 39C as SEQ ID NOS: 293-315.

FIGS. 6A-6C show several embodiments of anti-PD-L1 antibody variable domain sequences.

FIGS. 7A-7C depict three exemplary bispecific antitumor antagonists, Bi-TPM-93 (FIG. 7A), Bi-TPM-94A (FIG. 7B), and Bi-TPM-94B (FIG. 7C).

FIG. 8 summarizes the arrangement of functional domains in the bispecific antagonists depicted in FIGS. 7A-7C.

FIGS. 9A-9B show the heavy chain (HC) and light chain (LC) amino acid sequences corresponding to the bispecific antagonists depicted in FIGS. 7A-7C.

FIG. 10 depicts a blocking assay showing that Bi-TPM-94A blocks the interaction between PD-1 and its ligand (IC₅₀=0.15 nM), PD-L1 better than Bi-TPM-93 (IC₅₀=0.83 nM).

FIG. 11 shows a non-reducing PAGE analysis of Bi-TPM-94A and Bi-TPM-94B transiently expressed in human embryonic kidney (HEK) 293 cells.

FIG. 12 shows a size-exclusion ultra-high performance liquid chromatography (SE-UHPLC) analysis illustrating species heterogeneity in Bi-TPM-93 and Bi-TPM-94, which is eliminated by linker modification in Bi-TPM-94B.

FIG. 13A shows that the binding affinities of Bi-TPM-94A and Bi-TPM-94B for PD-1 are stronger than the binding affinity of a benchmark anti-PD-1 antibody for PD-1.

FIG. 13B shows that the binding affinities of Bi-TPM-94A and Bi-TPM-94B for TIGIT are stronger than the binding affinity of a benchmark anti-TIGIT antibody for TIGIT.

FIGS. 14A-14B show Bi-TPM-94A and Bi-TPM-94B potentially block both TIGIT binding to its ligand, human PVR (CD155) (FIG. 14A) and block PD-1 binding to its ligand, PD-L1 (FIG. 14B).

FIG. 15 shows the results of an ELISA assay demonstrating simultaneous binding of PD-1 and TIGIT by Bi-TPM-94A and Bi-TPM-94B in which huPD-1-Fc coated 96 well plates were incubated with serially diluted samples of Bi-TPM-94A and Bi-TPM-94B, followed by His-tagged huTIGIT protein, whereby bound molecules were detected using HRP-conjugated anti-His tag Ab and TMB substrate.

FIGS. 16A-16B show increased IFN-γ secretion from human PBMCs (Donor 287, FIG. 16A; Donor 401, FIG. 16B) with Bi-TPM-94B relative to the individual or combination of parental anti-PD-1 and anti-TIGIT antibodies, as well as the negative controls.

FIGS. 17A-17B show that Bi-TPM-94B enhances proliferation of primary human T cells from Donor 287 PBMCs (FIG. 17A) and Donor 401 PBMCs (FIG. 17B) to a greater extent than the individual or combination of parental anti-PD-1 and anti-TIGIT antibodies, as well as the negative controls.

FIG. 18 is a pharmacokinetic profile showing that Bi-TPM-94A and Bi-TPM-94B have similar in vivo half-lives (T_{1/2}) following a tail vein injection into 6-10 week old

3

female CD1 mice. The bispecific antagonists were recovered from serum taken at various times post-injection and subjected to analysis by ELISA.

FIG. 19A shows the heavy chain CDR sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A. FIG. 19B shows the light chain CDR sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A. The FR sequences flanking the anti-LAG-3 CDR sequences are listed in FIG. 39C as SEQ ID NOS: 316-337.

FIG. 20 shows the VH and VL sequences of anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A.

FIGS. 21A-21B show the results of assays confirming the ability of the anti-LAG-3 mAbs to block LAG-3 binding.

FIG. 22 shows the results of a cell-based blocking assay measuring the ability of the anti-LAG-3 mAb 2L2A.1, a benchmark (BM) anti-LAG-3 mAb, and a chimeric 2L2A antibody (SEQ ID NOS: 203 and 204) to block the interaction between LAG-3-muFc and its major ligand, major histocompatibility complex (MHC) antigen expressed on Raji cells. The assay data was used to calculate IC50 values (nm) depicted.

FIGS. 23A-23B show affinity analysis of anti-LAG-3 2L2A.1 mAb for binding human LAG-3-His (FIG. 23A) or human LAG-3-mIgG2a (FIG. 23B) as determined by surface plasmon resonance (SPR), along with corresponding binding affinity constants.

FIG. 24 depicts the binding of anti-LAG-3 mAb variant, 2L2A.1 or a benchmark antibody (BM) to LAG-3, including the half maximal effective concentrations (EC₅₀) producing a response halfway between the baseline and the maximum.

FIG. 25 shows a non-denaturing polyacrylamide gel (PAGE) analysis of humanized anti-LAG-3 mAb variant 2L2A.1 transiently expressed by HEK293. The positive control is HybPL1 (1PL11 CDRg-VH:1PL25 CDRg-VL).

FIG. 26 is a FACS analysis showing co-expression of LAG-3 and PD-1 in activated human CD3⁺ T cells.

FIGS. 27A-27B show IFN- γ production, PBMCs from two donors (Donor 0105, FIG. 27A; Donor 0817, FIG. 27B) were stimulated with *Staphylococcal enterotoxin B* (SEB; lanes 2-4) or not stimulated with SEB (lane 1) in a 96 well plate. Following stimulation, the donor PBMCs were incubated with: no antibody (lanes 1, 2), an anti-LAG-3 benchmark (BM) antibody (lane 3), or the anti-LAG-3 mAb, 2L2A.1. The results of this assay showed that 2L2A.1 induces more IFN- γ production in both donor PBMCs than the anti-LAG-3 benchmark antibody.

FIGS. 28A-28C show increased IFN- γ production from three donor human PBMCs (Donor 223, FIG. 28A; Donor 224, FIG. 28B; Donor 225, FIG. 28C) stimulated with SEB (lanes 2-4) or not stimulated with SEB (lane 1). In addition, the donor PBMCs were incubated with: no antibody (lanes 1, 2), an anti-LAG-3 benchmark (BM) antibody (lane 3) or with the anti-LAG-3 mAb 2L2A.1.

FIGS. 29A-29C show that the anti-LAG-3 mAb 2L2A.1 enhances proliferation of primary human T cells from Donor 223 (FIG. 29A), Donor 224 (FIG. 29B) and Donor 225 (FIG. 29C) to a greater extent than the benchmark anti-LAG-3 antibody.

FIGS. 30A-30B depict two exemplary bispecific antitumor antagonists, Bi-LT-1 (FIG. 30A) and Bi-LT-3 (FIG. 30B).

FIG. 31 summarizes the arrangement of functional domains in the bispecific antagonists depicted in FIGS. 30A-30B.

4

FIG. 32 show the heavy chain (HC) and light chain (LC) amino acid sequences corresponding to the bispecific antagonists depicted in FIGS. 30A-30B.

FIGS. 33A-33B shows the results of a cell-based blocking assay measuring the ability of the bispecific antagonists, LT-1 and LT-3, and the bispecific antagonist, Bi-TPM-94B or an anti-LAG-3 benchmark mAb to block the interaction between LAG-3-muFc and its major ligand, major histocompatibility complex (MHC) antigen expressed on Raji cells (FIG. 33A) or block the interaction between TIGIT and its ligand, human PVR (CD155) (FIG. 33B). The assay data was used to calculate IC50 values (nm) depicted.

FIG. 34 shows the results of an ELISA assay demonstrating simultaneous binding of LAG-3 and TIGIT by Bi-LT-1, Bi-LT-3 or the parental anti-LAG-3 mAb in which LAG-3-muFc coated 96 well plates were incubated with serially diluted samples of Bi-LT-1, Bi-LT-3 or the parental anti-LAG-3 mAb, followed by His-tagged huTIGIT protein, whereby bound molecules were detected using HRP-conjugated anti-His tag HRP and TMB substrate. The assay data was used to calculate EC50 values (nm) depicted.

FIGS. 35A-35D depict pharmacokinetic profiles and in vivo half-lives (T_{1/2}) corresponding to the parental anti-LAG-3 mAb (FIG. 35A), an anti-LAG-3 benchmark mAb (FIG. 35B), Bi-LT-1 (FIG. 35C), or Bi-LT-3 (FIG. 35D) following a tail vein injection into 6-10 week old female CD1 mice. The antibodies and bispecific antagonists were recovered from serum taken at various times post-injection and subjected to analysis by ELISA. The T_{1/2} for parental anti-LAG-3 mAb, Bi-LT-1 and Bi-LT-3 are five to six days, the T_{1/2} for anti-LAG-3 BM mAb is either 2 days (mouse 3) or 7 days (mouse 4).

FIG. 36A shows a size exclusion chromatography (SEC) profile of Bi-LT-1 and Bi-LT-3 showing homogeneity and good stability at 4° C. after 7 days. FIG. 36B shows a size-exclusion ultra-high performance liquid chromatography (SE-UHPLC) analysis illustrating species homogeneity of protein A purified Bi-LT-1 and Bi-LT-3, as reflected in low levels of high molecular weight (HMW) species at Day 0 and Day 7 (1.3%, 1.5% respectively for Bi-LT-1 and 1.3%, 1.4%, respectively for Bi-LT-3) and low molecular weight (LMW) species at Day 0 and Day 7 (0.2%, 0.2%, respectively for Bi-LT-1 and 0.3%, 0.5%, respectively for Bi-LT-3) in comparison to dimer species at Day 0 and Day 7 (98.4%, 98.3%, respectively for Bi-LT-1 and 98.4%, 98.1%, respectively for Bi-LT-3).

FIGS. 37A-37B show IFN- γ production from human PBMCs stimulated with *Staphylococcal enterotoxin B* (SEB; lanes 2-8) or not stimulated with SEB (lane 1) in the presence of SHP-77 cells (FIG. 37A) or H358 cells (FIG. 37B), followed by incubation with: no antibody (lanes 1, 2); human IgG (lane 3); parental anti-TIGIT B21-35 mAb (lane 4); parental anti-LAG-3 2L2A.1 mAb (lane 5); parental mAbs, anti-TIGIT B21-35 and anti-LAG-3 2L2A.1 mAb (lane 6); Bi-LT-1 (lane 7); and Bi-LT-3 (lane 8).

FIG. 38 shows the proliferation of CD4 T cells from human PBMCs stimulated with SEB in the presence of SHP-77 cells (lanes 2-8) and human IgG control (lane 3), anti-TIGIT mAb B21-35 (lane 4), anti-LAG-3 mAb (lane 5), the combination of anti-TIGIT mAb and anti-LAG-3 mAb (lane 6), Bi-LT-1 (lane 7) or Bi-LT-3 (lane 8).

FIG. 39A shows the framework regions (FRs) corresponding to the anti-TIGIT CDRs in FIG. 1. FIG. 39B shows the FRs corresponding to the anti-PD-1 CDRs in FIG. 3. FIG. 39C shows the FRs corresponding to the anti-PD-L1 CDRs in FIG. 5 and the FRs corresponding to the anti-LAG-3 CDR in FIGS. 19A and 19B.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed method and compositions belong. It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “a peptide” includes “one or more” peptides or a “plurality” of such peptides. With respect to the teachings in the present application, any issued patent or patent application publication described in this application is expressly incorporated by reference herein.

As used herein, the term “TIGIT” refers to any form of TIGIT and variants thereof that retain at least part of the activity of TIGIT. Unless indicated differently, such as by specific reference to human TIGIT, TIGIT includes all mammalian species of native sequence TIGIT, e.g., human, canine, feline, equine, and bovine.

As used herein, the term “PD-1” refers to any form of PD-1 and variants thereof that retain at least part of the activity of PD-1. Unless indicated differently, such as by specific reference to human PD-1, PD-1 includes all mammalian species of native sequence PD-1, e.g., human, canine, feline, equine, and bovine.

As used herein, the term “PD-L1” refers to any form of PD-L1 and variants thereof that retain at least part of the activity of PD-L1. Unless indicated differently, such as by specific reference to human PD-L1, PD-L1 includes all mammalian species of native sequence PD-L1, e.g., human, canine, feline, equine, and bovine.

The term “agonist” refers to a substance which promotes (i.e., induces, causes, enhances, or increases) the biological activity or effect of another molecule. The term agonist encompasses substances which bind receptor, such as an antibody, and substances which promote receptor function without binding thereto (e.g., by activating an associated protein).

The term “antagonist” or “inhibitor” refers to a substance that prevents, blocks, inhibits, neutralizes, or reduces a biological activity or effect of another molecule, such as a receptor or ligand. An antagonist can be a monospecific antibody or a bispecific antibody.

As used herein, the term “antibody” refers to a polypeptide or a polypeptide complex that specifically recognizes and binds to an antigen through one or more immunoglobulin variable regions. An antibody can be a whole antibody, an antigen binding fragment or a single chain thereof. The term “antibody” encompasses various broad classes of polypeptides that can be distinguished biochemically. Those skilled in the art will appreciate that heavy chains are classified as alpha, delta, epsilon, gamma, and mu, or α , δ , ϵ , γ and μ with some subclasses among them (e.g., $\gamma 1$ - $\gamma 4$). It is the nature of this chain that determines the “class” of the antibody as IgG, IgM, IgA, IgE, or IgD, respectively. The immunoglobulin subclasses (isotypes) e.g., IgG1, IgG2, IgG3, IgG4, etc. are well characterized and are known to confer functional specialization. Modified versions of each of these classes and isotypes are readily discernible to the skilled artisan in view of the instant disclosure and, accordingly, are within the scope of the instant disclosure. All immunoglobulin classes are within the scope of the present disclosure, the following discussion will generally be directed to the IgG class of immunoglobulin molecules.

Antibodies of the disclosure include, but are not limited to, polyclonal, monoclonal, multispecific, bispecific, human, humanized, primatized, chimeric and single chain antibodies. Antibodies disclosed herein may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine, rat, donkey, rabbit, goat, guinea pig, camel, llama, horse, or chicken antibodies. In some embodiments, the variable region may be chondrichthoid in origin (e.g., from sharks).

The terms “antibody fragment” and “antigen-binding fragment” are used with reference to a portion of an antibody, such as F(ab')₂, F(ab)₂, Fab', Fab, Fv, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv), fragments comprising either a VL or VH domain, fragments produced by a Fab expression library, and anti-idiotypic (anti-Id) antibodies. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the intact antibody. The term “antibody fragment” includes DARTs, and diabodies. The term “antibody fragment” also includes any synthetic or genetically engineered proteins comprising immunoglobulin variable regions that act like an antibody by binding to a specific antigen to form a complex. A “single-chain fragment variable” or “scFv” refers to a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins. In some aspects, the regions are connected with a short linker peptide of ten to about 25 amino acids. The linker can be rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker. With regard to IgGs, a standard immunoglobulin molecule comprises two identical light chain polypeptides of molecular weight approximately 23,000 Daltons, and two identical heavy chain polypeptides of molecular weight 53,000-70,000. The four chains are typically joined by disulfide bonds in a “Y” configuration where the light chains bracket the heavy chains starting at the mouth of the “Y” and continuing through the variable region.

Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention, the numbering of the constant region domains in conventional antibodies increases as they become more distal from the antigen-binding site or amino-terminus of the antibody. In conventional antibodies, the N-terminal portion is a variable region and at the C-terminal portion is a constant region; the CH3 and CL domains actually comprise the carboxy-terminus of the heavy and light chain, respectively.

As indicated above, the variable region allows the antibody to selectively recognize and specifically bind epitopes on antigens. That is, the VL domain and VH domain, or subset of the complementarity determining regions (CDRs), of an antibody combine to form the variable region that defines a three dimensional antigen-binding site. This quaternary antibody structure forms the antigen-binding site present at the end of each arm of the Y. More specifically, the antigen-binding site is defined by three CDRs on each of the VH and VL chains (i.e. HCDR1, HCDR2, HCDR3, LCDR1,

LCDR2 and LCDR3). In some instances, e.g., certain immunoglobulin molecules are derived from camelid species or engineered based on camelid immunoglobulins. Alternatively, an immunoglobulin molecule may consist of heavy chains only with no light chains or light chains only with no heavy chains.

In naturally occurring antibodies, the six CDRs present in each antigen-binding domain are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The remainder of the amino acids in the antigen-binding domains, referred to as “framework” regions, show less inter-molecular variability. The framework regions largely adopt a β -sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β -sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids comprising the CDRs and the framework regions, respectively, can be readily identified for any given heavy or light chain variable region by one of ordinary skill in the art, since they have been precisely defined.

As used herein, the terms “VH1” and “VH2” refer to immunoglobulin heavy chain variable domains corresponding to two different binding specificities. Likewise, the terms “VL1” and “VL2” refer to light chain variable domains corresponding to two different binding specificities. When used together, it is to be understood that VH1 and VL1 regions define a common binding specificity and that VH2 and VL2 domains define a second binding specificity.

The term “framework region (FR)” as used herein refers to variable domain residues other than the CDR residues. Each variable domain typically has four FRs flanking the corresponding CDRs. For example, a VH domain typically has four HFRs: HFR1, HFR2, HFR3 and HFR4 flanking the three HCDRs in the configuration of HFR1-HCDR1-HFR2-HCDR2-HFR3-HCDR3-HFR4. Similarly, an LH domain typically has four LFRs flanking the three LCDRs in the configuration of: LFR1-LCDR1-LFR2-LCDR2-LFR3-LCDR3-LFR4. Exemplary FRs that may be utilized in the antagonists described herein are summarized in FIGS. 39A-39C.

Light chains are classified as either kappa or lambda (K , λ). Each heavy chain class may be bound with either a kappa or lambda light chain. In general, the light and heavy chains are covalently bonded to each other, and the “tail” portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated either by hybridomas, B cells or genetically engineered host cells. In the heavy chain, the amino acid sequences run from an N-terminus at the forked ends of the Y configuration to the C-terminus at the bottom of each chain.

As used herein, the terms “light chain constant region” or “CL” are used interchangeably herein with reference to amino acid sequences derived from antibody light chain. Preferably, the light chain constant region comprises at least one of a constant kappa domain or constant lambda domain.

As used herein, the term “heavy chain constant region” includes amino acid sequences derived from an immunoglobulin heavy chain. A polypeptide comprising a heavy chain constant region comprises at least one of: a CH1

domain, a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant or fragment thereof. For example, an antigen-binding polypeptide for use in the disclosure may comprise a polypeptide chain comprising a CH1 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH2 domain; a polypeptide chain comprising a CH1 domain and a CH3 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH3 domain, or a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, a CH2 domain, and a CH3 domain. In some embodiments, a polypeptide of the disclosure comprises a polypeptide chain comprising a CH3 domain. Further, an antibody for use in the disclosure may lack at least a portion of a CH2 domain (e.g., all or part of a CH2 domain). It should be understood that the heavy chain constant region may be modified such that they vary in amino acid sequence from the naturally occurring immunoglobulin molecule. For example, the inventors of the present application have found that an Fc loop in the CH3 domain can tolerate or accommodate significant insertions (e.g., greater than 100 aa).

The heavy chain constant region of an antibody disclosed herein may be derived from different immunoglobulin molecules. For example, a heavy chain constant region of a polypeptide may comprise a CH1 domain derived from an IgG1 molecule and a hinge region derived from an IgG3 molecule. In another example, a heavy chain constant region can comprise a hinge region derived, in part, from an IgG1 molecule and, in part, from an IgG3 molecule. In another example, a heavy chain portion can comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule.

A “light chain-heavy chain pair” refers to the collection of a light chain and heavy chain that can form a dimer through a disulfide bond between the CL domain of the light chain and the CH1 domain of the heavy chain.

The subunit structures and three dimensional configurations of the constant regions of the various immunoglobulin classes are well known. As used herein, the term “VH domain” includes the amino terminal variable domain of an immunoglobulin heavy chain and the term “CH1 domain” includes the first (most amino terminal) constant region domain of an immunoglobulin heavy chain. The CH1 domain is adjacent to the VH domain and is amino terminal to the hinge region of an immunoglobulin heavy chain molecule.

As used herein the term “CH2 domain” includes the portion of a heavy chain molecule that extends, e.g., from about residue 244 to residue 360 of an antibody using conventional numbering schemes (residues 244 to 360, Kabat numbering system; and residues 231-340, EU numbering system). The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. The CH3 domain extends from the CH2 domain to the C-terminal of the IgG molecule and comprises approximately 108 residues.

As used herein, the term “hinge region” includes the portion of a heavy chain molecule that joins the CH1 domain to the CH2 domain. This hinge region comprises approximately 25 residues and is flexible, thus allowing the two N-terminal antigen-binding regions to move independently. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains.

As used herein the term “disulfide bond” includes a covalent bond formed between two sulfur atoms. The amino acid cysteine comprises a thiol group that can form a disulfide bond or bridge with a second thiol group. In most naturally occurring IgG molecules, the CH1 and CL regions are linked by a disulfide bond and the two heavy chains are linked by two disulfide bonds at positions corresponding to 239 and 242 using the Kabat numbering system (position 226 or 229, EU numbering system).

As used herein, a “variant” of antibody, antibody fragment or antibody domain refers to antibody, antibody fragment or antibody domain that (1) shares a sequence identity of at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with the original antibody, antibody fragment or antibody domain, and (2) binds specifically to the same target that the original antibody, antibody fragment or antibody domain binds specifically. It should be understood that where a measure of sequence identity is presented in the form of the phrase “at least x % identical” or “at least x % identity”, such an embodiment includes any and all whole number percentages equal to or above the lower limit. Further it should be understood that where an amino acid sequence is presented in the present application, it should be construed as additionally disclosing or embracing amino acid sequences having a sequence identity of at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity to that amino acid sequence.

As used herein, the phrase “humanized antibody” refers to an antibody derived from a non-human antibody, typically a mouse monoclonal antibody. Alternatively, a humanized antibody may be derived from a chimeric antibody that retains or substantially retains the antigen binding properties of the parental, non-human, antibody but which exhibits diminished immunogenicity as compared to the parental antibody when administered to humans.

As used herein, the phrase “chimeric antibody,” refers to an antibody where the immunoreactive region or site is obtained or derived from a first species and the constant region (which may be intact, partial or modified in accordance with the instant disclosure) is obtained from a second species. In certain embodiments the target binding region or site will be from a non-human source (e.g., mouse or primate) and the constant region is human.

Included within the scope of the multispecific antibodies of the present application are various compositions and methodologies, including asymmetric IgG-like antibodies (e.g., triomab/quadroma, Trion Pharma/Fresenius Biotech); knobs-into-holes antibodies (Genentech); Cross MAbs (Roche); electrostatically matched antibodies (AMGEN); LUZ-Y (Genentech); strand exchange engineered domain (SEED) body (EMD Serono; biologic, Merus); Fab-exchanged antibodies (Genmab), symmetric IgG-like antibodies (e.g. dual targeting (DT)-Ig (GSK/Domantis); two-in-one antibody (Genentech); crosslinked MAbs (Karmanos Cancer Center), mAb2 (F-star); Cov X-body (Cov X/Pfizer); dual variable domain (DVD)-Ig fusions (Abbott); IgG-like bispecific antibodies (Eli Lilly); Ts2Ab (Medimmune/AZ); BsAb (ZymoGenetics); HERCULES (Biogen Idec, TvaAb, Roche); scFv/Fc fusions; SCORPION (Emergent BioSolutions/Trubion, ZymoGenetics/BMS); dual affinity retargeting technology (Fc-DART), MacroGenics; dual (scFv)2-Fabs (National Research Center for Antibody Medicine); F(ab)2 fusions (Medarex/AMGEN); dual-action or Bis-Fab (Genentech); Dock-and-Lock (DNL, ImmunoMedics); Fab-Fv (UCB-Celltech); scFv- and diabody-based antibodies (e.g., bispecific T cell engagers (BiTEs, Micromet); tandem

diabodies (Tandab, Affimed); DARTs (MacroGenics); single-chain diabodies; TCR-like antibodies (AIT, Receptor Logics); human serum albumin scFv fusion (Merrimack); COMBODIES (Epigen Biotech); and IgG/non-IgG fusions (e.g., immunocytokines (EMDSerono, Philogen, ImmunoGene, ImmunoMedics).

By “specifically binds” or “has specificity to”, it is generally meant that an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. According to this definition, an antibody is said to “specifically bind” to an epitope when it binds to that epitope via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. The term “specificity” is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody “A” may be deemed to have a higher specificity for a given epitope than antibody “B,” or antibody “A” may be said to bind to epitope “C” with a higher specificity than it has for related epitope “D.” In some embodiments, an antibody or an antibody fragment “has specificity to” an antigen if the antibody or antibody fragment forms a complex with the antigen with a dissociation constant (K_d) of 10^{-6} M or less, 10^{-7} M or less, 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M or less.

As used herein, the phrase “chimeric antibody,” refers to an antibody where the immunoreactive region or site is obtained or derived from a first species and the constant region (which may be intact, partial or modified in accordance with the instant disclosure) is obtained from a second species. In certain embodiments the target binding region or site will be from a non-human source (e.g., mouse or primate) and the constant region is human.

The term “antagonist antibody” refers to an antibody that binds to a target and prevents or reduces the biological effect of that target. In some embodiments, the term can denote an antibody that prevents the target, e.g., TIGIT, to which it is bound from performing a biological function.

As used herein, an “anti-PD-1 antagonist antibody” refers to an antibody that is able to inhibit PD-1 biological activity and/or downstream events(s) mediated by PD-1. Anti-PD-1 antagonist antibodies encompass antibodies that block, antagonize, suppress or reduce (to any degree including significantly) PD-1 biological activity, including downstream events mediated by PD-1, such as PD-1 binding and downstream signaling, inhibition of T cell proliferation, inhibition of T cell activation, inhibition of IFN secretion, inhibition of IL-2 secretion, inhibition of TNF secretion, induction of IL-10, and inhibition of anti-tumor immune responses. For purposes of the present invention, it will be explicitly understood that the term “anti-PD-1 antagonist antibody” (interchangeably termed “antagonist PD-1 antibody”, “antagonist anti-PD-1 antibody” or “PD-1 antagonist antibody”) encompasses all the previously identified terms, titles, and functional states and characteristics whereby PD-1 itself, a PD-1 biological activity, or the consequences of the biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree. In some embodiments, an anti-PD-1 antagonist antibody binds PD-1 and upregulates an anti-tumor immune response.

As used herein, an “anti-PD-L1 antagonist antibody” refers to an antibody that is able to inhibit PD-L1 biological activity and/or downstream events(s) mediated by PD-L1. Anti-PD-L1 antagonist antibodies encompass antibodies that block, antagonize, suppress or reduce (to any degree including significantly) PD-L1 biological activity, including downstream events mediated by PD-L1, such as PD-L1

11

binding and downstream signaling, inhibition of T cell proliferation, inhibition of T cell activation, inhibition of IFN secretion, inhibition of IL-2 secretion, inhibition of TNF secretion, induction of IL-10, and inhibition of anti-tumor immune responses. For purposes of the present invention, it will be explicitly understood that the term “anti-PD-L1 antagonist antibody” (interchangeably termed “antagonist PD-L1 antibody”, “antagonist anti-PD-L1 antibody” or “PD-L1 antagonist antibody”) encompasses all the previously identified terms, titles, and functional states and characteristics whereby PD-L1 itself, a PD-L1 biological activity, or the consequences of the biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree. In some embodiments, an anti-PD-L1 antagonist antibody binds PD-L1 and upregulates an anti-tumor immune response.

The phrase “immune checkpoint regulator” refers to a functional class of agents, which inhibit or stimulate signaling through an immune checkpoint. An “immune checkpoint regulator” includes receptors and their associated ligands, which together provide a means for inhibiting or stimulating signaling pathways that otherwise lead to T-cell activation. Exemplary immune checkpoint regulators include, but are not limited to, TIGIT and its CD155 ligand, PVR; PD-1 and its ligands, PD-L1 and PD-L2; CTLA-4 and its ligands, B7-1 and B7-2; TIM-3 and its ligand, Galectin-9; LAG-3 and its ligands, including liver sinusoidal endothelial cell lectin (LSECtin) and Galectin-3; CD122 and its CD122R ligand; CD70, B7H3, B and T lymphocyte attenuator (BTLA), and VISTA.

The phrases “checkpoint regulator antagonist”, “immune checkpoint binding antagonist” and “immune checkpoint antagonist” are used interchangeably herein with reference to a class of agents that interfere with (or inhibit) the activity of an immune checkpoint regulator so that, as a result of the binding to the checkpoint regulator or its ligand, signaling through the checkpoint regulator receptor is blocked or inhibited. By inhibiting this signaling, immune-suppression can be reversed so that T cell immunity against cancer cells can be re-established or enhanced. Immune checkpoint regulator antagonists include antibody fragments, peptide inhibitors, dominant negative peptides and small molecule drugs, either in isolated forms or as part of a fusion protein or conjugate.

The phrases “immune checkpoint binding agonist” and “immune checkpoint agonist” are used interchangeably herein with reference to a class of agents that stimulate the activity of an immune checkpoint regulator so that, as a result of the binding to the checkpoint regulator or its ligand, signaling through the checkpoint regulator receptor is stimulated. By stimulating this signaling, T cell immunity against cancer cells can be re-established or enhanced. Exemplary immune checkpoint regulator agonists include, but are not limited to members of the tumor necrosis factor (TNF) receptor superfamily, such as CD27, CD40, OX40 (CD 134), glucocorticoid-induced TNFR family-related protein (GITR), and 4-1BB (CD137) and their ligands. Additional checkpoint regulator agonists belong to the B7-CD28 superfamily, including CD28 and ICOS.

The phrases “dominant-negative protein” or “dominant-negative peptide” refer to a protein or peptide derived from a wild type protein that has been genetically modified by mutation and/or deletion so that the modified protein or peptide interferes with the function of the endogenous wild-type protein from which it is derived.

The phrase “small molecule drug” refers to a molecular entity, often organic or organometallic, that is not a polymer,

12

that has medicinal activity, and that has a molecular weight less than about 2 kDa, less than about 1 kDa, less than about 900 Da, less than about 800 Da or less than about 700 Da. The term encompasses most medicinal compounds termed “drugs” other than protein or nucleic acids, although a small peptide or nucleic acid analog can be considered a small molecule drug. Examples include chemotherapeutic anticancer drugs and enzymatic inhibitors. Small molecule drugs can be derived synthetically, semi-synthetically (i.e., from naturally occurring precursors), or biologically.

When describing polypeptide domain arrangements with hyphens between individual domains (e.g., CH2-CH3), it should be understood that the order of the listed domains is from the amino terminal end to the carboxy terminal end.

By “specifically binds” or “has specificity to”, it is generally meant that an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. According to this definition, an antibody is said to “specifically bind” to an epitope when it binds to that epitope via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. The term “specificity” is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody “A” may be deemed to have a higher specificity for a given epitope than antibody “B,” or antibody “A” may be said to bind to epitope “C” with a higher specificity than it has for related epitope “D.”

The term “immunoconjugate” refers to an antibody which is fused by covalent linkage to an inhibitory peptide or small molecule drug. The peptide or small molecule drug can be linked to the C-terminus of a constant heavy chain or to the N-terminus of a variable light and/or heavy chain.

A “linker” may be used to link the peptide or small molecule drug, such as a maytansinoid, to the antitumor antagonists in a stable, covalent manner. Linkers can be susceptible to or be substantially resistant to acid-induced cleavage, light-induced cleavage, peptidase-induced cleavage, esterase-induced cleavage, and disulfide bond cleavage, at conditions under which the compound or the antibody remains active. Suitable linkers are well known in the art and include, for example, disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups and esterase labile groups. Linkers also include charged linkers, and hydrophilic forms thereof as described herein and known in the art. The immunoconjugate may further include a flexible 3-15 amino acid peptide (or spacer) between an antitumor antagonist and the peptide and/or small molecule drug.

As used herein, the term “immunoglobulin scaffold”, refers to any polymer of amino acids that exhibits properties desired to support the function of an antagonist, including addition of antibody specificity, enhancement of antibody function or support of antibody structure and stability. An immunoglobulin scaffold may have one or more immunoglobulin constant regions, including CH1, CH2, and/or CH3 regions from an immunoglobulin heavy chain and/or a CL region from an immunoglobulin light chain. The immunoglobulin scaffold can be grafted with binding domains of a donor polypeptide to confer the binding specificity of the donor polypeptide onto the scaffold.

As used herein, the phrase “multispecific inhibitor” refers to a molecule comprising at least two targeting domains with different binding specificities. In some embodiments, the multispecific inhibitor is a polypeptide comprising a scaffold and two or more immunoglobulin antigen binding domains

targeting different antigens or epitopes. In certain embodiments, the multispecific inhibitor is a bispecific antibody.

As used herein, the phrase “bispecific” refers to a molecule comprising at least two targeting domains with different binding specificities. Each targeting domain is capable of binding specifically to a target molecule and inhibiting a biological function of the target molecule upon binding to the target molecule. In some embodiments, the bispecific checkpoint regulator antagonist is a polymeric molecule having two or more peptides. In some embodiments, the targeting domain comprises an antigen binding domain or a CDR of an antibody. In some embodiments, the bispecific inhibitor is a bispecific antibody.

The terms “bispecific antibody,” and “bispecific antagonist” are used interchangeably herein with reference to an antibody that can specifically bind two different antigens (or epitopes). In some embodiments, the bispecific antibody is a full-length antibody that binds one antigen (or epitope) on one of its two binding arms (one pair of HC/LC), and binds a different antigen (or epitope) on its second arm (a different pair of HC/LC). In these embodiments, the bispecific antibody has two distinct antigen binding arms (in both specificity and CDR sequences), and is monovalent for each antigen it binds to.

In other embodiments, the bispecific antibody is a full-length antibody that can bind two different antigens (or epitopes) in each of its two binding arms (two pairs of HC/LC). In these embodiments, the bispecific antibody has two identical antigen binding arms, with identical specificity and identical CDR sequences, and is bivalent for each antigen it binds to.

Exemplary bispecific antibodies may include asymmetric IgG-like antibodies (e.g., triomab/quadroma, Trion Pharma/Fresenius Biotech); knobs-into-holes antibodies (Genentech); Cross MAbs (Roche); electrostatically matched antibodies (AMGEN); LUZ-Y (Genentech); strand exchange engineered domain (SEED) body (EMD Serono; biologic, Merus); Fab-exchanged antibodies (Genmab), symmetric IgG-like antibodies (e.g. dual targeting (DT)-Ig (GSK/Domantis); two-in-one antibody (Genentech); crosslinked MAbs (Karmanos Cancer Center), mAb2 (F-star); Cov X-body (Cov X/Pfizer); dual variable domain (DVD)-Ig fusions (Abbott); IgG-like bispecific antibodies (Eli Lilly); Ts2Ab (Medimmune/AZ); BsAb (ZymoGenetics); HERCULES (Biogen Idec, TvAb, Roche); scFv/Fc fusions; SCORPION (Emergent BioSolutions/Trubion, ZymoGenetics/BMS); dual affinity retargeting technology (Fc-DART), MacroGenics; dual (scFv)2-Fabs (National Research Center for Antibody Medicine); F(ab)2 fusions (Medarex/AMGEN); dual-action or Bis-Fab (Genentech); Dock-and-Lock (DNL, ImmunoMedics); Fab-Fv (UCB-Celltech); scFv- and diabody-based antibodies (e.g., bispecific T cell engagers (BiTEs, Micromet); tandem diabodies (Tandab, Affimed); DARTs (MacroGenics); single-chain diabodies; TCR-like antibodies (AIT, Receptor Logics); human serum albumin scFv fusion (Merrimack); COMBODIES (Epigen Biotech); and IgG/non-IgG fusions (e.g., immunocytokines (EMD Serono, Philogen, ImmunoGene, ImmunoMedics).

The terms “treat” and “treatment” refer to the amelioration of one or more symptoms associated with a cell proliferative disorder; prevention or delay of the onset of one or more symptoms of a cell proliferative disorder; and/or lessening of the severity or frequency of one or more symptoms of cell proliferative disorder.

The phrases “to a patient in need thereof”, “to a patient in need of treatment” or “a subject in need of treatment” includes subjects, such as mammalian subjects, that would

benefit from administration of the antitumor antagonist of the present disclosure for treatment of a cell proliferative disorder.

The terms “therapeutically effective amount”, “pharmacologically effective amount”, and “physiologically effective amount” are used interchangeably to mean the amount of an antitumor antagonist that is needed to provide a threshold level of active antagonist agents in the bloodstream or in the target tissue. The precise amount will depend upon numerous factors, e.g., the particular active agent, the components and physical characteristics of the composition, intended patient population, patient considerations, and the like, and can readily be determined by one skilled in the art, based upon the information provided herein or otherwise available in the relevant literature.

The terms, “improve”, “increase” or “reduce”, as used in this context, indicate values or parameters relative to a baseline measurement, such as a measurement in the same individual prior to initiation of the treatment described herein, or a measurement in a control individual (or multiple control individuals) in the absence of the treatment described herein.

A “control individual” is an individual afflicted with the same cell proliferative disorder as the individual being treated, who is about the same age as the individual being treated (to ensure that the stages of the disease in the treated individual and the control individual(s) are comparable). The individual (also referred to as “patient” or “subject”) being treated may be a fetus, infant, child, adolescent, or adult human with a cell proliferative disorder.

The term “cell proliferative disorder” refers to a disorder characterized by abnormal proliferation of cells. A proliferative disorder does not imply any limitation with respect to the rate of cell growth, but merely indicates loss of normal controls that affect growth and cell division. Thus, in some embodiments, cells of a proliferative disorder can have the same cell division rates as normal cells but do not respond to signals that limit such growth. Within the ambit of “cell proliferative disorder” is a neoplasm, cancer or tumor.

The term “cancer” or “tumor” refers to any one of a variety of malignant neoplasms characterized by the proliferation of cells that have the capability to invade surrounding tissue and/or metastasize to new colonization sites, and includes leukemia, lymphoma, carcinoma, melanoma, sarcoma, germ cell tumor and blastoma. Exemplary cancers for treatment with the methods of the instant disclosure include cancer of the brain, bladder, breast, cervix, colon, head and neck, kidney, lung, non-small cell lung, mesothelioma, ovary, prostate, stomach and uterus, leukemia, and medulloblastoma.

The term “leukemia” refers to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Exemplary leukemias include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemetic leukemia, basophilic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross’ leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leuke-

mia, mast cell leukemia, megakaryocytic leukemia, micro-myeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

The term "carcinoma" refers to the malignant growth of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas include, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriiform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiennoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma giganto-cellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, pre-invasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma villosum.

The term "sarcoma" refers to a tumor made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Exemplary sarcomas include, for example, chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lympho-

mas (e.g., Non-Hodgkin Lymphoma), immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectaltic sarcoma.

The term "melanoma" refers to a tumor arising from the melanocytic system of the skin and other organs. Melanomas include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma subungual melanoma, and superficial spreading melanoma.

Additional cancers include, for example, Hodgkin's Disease, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, small-cell lung tumors, primary brain tumors, stomach cancer, colon cancer, malignant pancreatic insulanoma, malignant carcinoid, premalignant skin lesions, testicular cancer, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, cervical cancer, endometrial cancer, and adrenal cortical cancer.

I. Checkpoint Regulator Antagonists

In one aspect, the present application provides an antitumor antagonist comprising an immunoglobulin scaffold with (1) a pair of arms containing variable domain regions that specifically bind to a first immune checkpoint regulator and (2) a single chain (scFv) that specifically binds to a second immune checkpoint regulator.

In another aspect, the present application provides an antitumor antagonist comprising an immunoglobulin scaffold structurally linked to both a first immune checkpoint regulator antagonist, and a second immune checkpoint regulator antagonist in the form of an scFv.

In both aspects, the immunoglobulin scaffold may comprise one or more immunoglobulin constant regions, e.g., IgG CH1, CH2, and/or CH3. In certain embodiments, the immunoglobulin scaffold is an Fc (hinge-CH2-CH3).

In some embodiments, the antitumor antagonist comprises an immunoglobulin scaffold in which the N-terminal end of the antagonist includes a first immune checkpoint regulator antagonist structurally linked thereto in which the first immune checkpoint regulator antagonist specifically binds to PD-1, PD-L1, LAG-3, TIGIT, and a second immune checkpoint regulator antagonist is positioned at the C-terminal end of the antagonist as an scFv that specifically binds to PD-1, PD-L1, LAG-3 or TIGIT.

In some embodiments, the scFv comprises a linker joining heavy chain variable regions to light chain variable regions. In one embodiment, the linker comprises an amino acid sequence comprising between 3, 4, 5, 6, 7, 8, 9, or 10 copies of the amino acid sequence G4S. In another embodiment, the linker comprises an amino acid sequence set forth in either one of SEQ ID NOS: 188-191. In a more particular embodiment, the linker comprises the amino acid sequence of SEQ ID NO: 191.

In one embodiment, the anti-TIGIT scFv comprises one or more heavy chain CDRs selected from SEQ ID NOS: 1-25 and one or more light chain CDRs selected from SEQ ID NOS: 26-47.

In another embodiment, the anti-TIGIT scFv comprising heavy chain/light chain variable regions, wherein the scFv has a heavy chain variable region (HCVR) having at least

80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 48, 50, 52, 54, 56, 58, 60, 62, 64, and 66 and a light chain variable region (LCVR) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% to an LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOS: 49, 51, 53, 55, 57, 59, 61, 63, and 67.

In a more particular embodiment, the anti-TIGIT scFv comprises an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO:66 and an LCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% to an LCVR having the amino acid sequence of SEQ ID NO:67.

In another embodiment, the anti-TIGIT scFv includes: an HCVR that comprises (1) an HCDR1 of SEQ ID NO:23, an HCDR2 of SEQ ID NO:24 and an HCDR3 of SEQ ID NO:25 in combination with (2) an HFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:260, an HFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:247, an HFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:261, and an HFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:236; and further includes an immunoglobulin LCVR that comprises (1) an LCDR1 of SEQ ID NO:45, an LCDR2 of SEQ ID NO:46 and an LCDR3 of SEQ ID NO:47 in combination with (2) an LFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:220, an LFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:228, an LFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:234, an LFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:262.

In another embodiment, the first targeting domain comprises one or more variable regions from an anti-PD-1 antibody, and the second targeting domain comprises an anti-TIGIT scFv as described above.

In one embodiment, the anti-PD-1 targeting domain comprises one or more heavy chain CDRs selected from SEQ ID NOS: 68-81 and/or one or more light chain CDRs selected from SEQ ID NOS: 82-95.

In another embodiment, the anti-PD-1 targeting domain comprises: an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 96, 98, 100, 102, 104, and 106; an LCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOS: 97, 99, 101, 103, 105, and 107; or both.

In another embodiment, the anti-PD-1 targeting domain includes: an HCVR that comprises (1) an HCDR1 of SEQ ID NO:79, an HCDR2 of SEQ ID NO:80 and an HCDR3 of SEQ ID NO:81 in combination with (2) an HFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:283, an HFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:277, an HFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:288, an HFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:274; an immunoglobulin LCVR that comprises (1) an LCDR1 of SEQ ID NO:93, an LCDR2 of SEQ ID NO:94 and an LCDR3 of SEQ ID NO:95 in combination with (2) an LFR1 having at least 80%, 85% or

90% identity to the amino acid sequence of SEQ ID NO:289, an LFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:290, an LFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:291, and an LFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:292; or both.

In another embodiment, the anti-PD-1 targeting domain comprises an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO:106; an LCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 107; or both.

In a particular embodiment, a bispecific anti-PD-1/anti-TIGIT antagonist includes a first targeting domain comprising an HCVR having the amino acid sequence of SEQ ID NO:106 and/or an LCVR having the amino acid sequence of SEQ ID NO:107 in combination with an anti-TIGIT scFv comprising an HCVR having the amino acid sequence of SEQ ID NO:66 and an LCVR having the amino acid sequence of SEQ ID NO:67.

In a more particular embodiment, the scFv in the bispecific anti-PD-1/anti-TIGIT antagonist comprises a linker joining heavy chain variable regions to light chain variable regions in the second targeting domain, where the linker comprises the amino acid sequence of SEQ ID NO:191.

In another embodiment, the bispecific anti-PD-1/anti-TIGIT antagonist includes: an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO:160; an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO:161; or both.

In another embodiment, the bispecific anti-PD-1/anti-TIGIT antagonist includes: an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO:162; an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO:161; or both.

In another embodiment, the bispecific anti-PD-1/anti-TIGIT antagonist comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 160, and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 161.

In another embodiment, the first targeting domain comprises one or more variable regions from an anti-PD-L1 antibody, and the second targeting domain comprises an anti-TIGIT scFv as described above.

In one embodiment, the anti-PD-L1 targeting domain comprises one or more heavy chain CDRs selected from SEQ ID NOS: 108-122 and/or one or more light chain CDRs selected from SEQ ID NOS: 123-138.

In another embodiment, the anti-PD-L1 targeting domain comprises an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 139, 141, 143, 145, 147, 149, 151, and 153 and/or an LCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 140, 142, 144, 146, 148, 152, and 154.

In another embodiment, the anti-PD-L1 targeting domain comprises an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to the amino acid sequence of SEQ ID NO:153 and/or an LCDR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an LCVR having the amino acid sequence of SEQ ID NO:154.

In another embodiment, the anti-PD-L1 targeting domain includes: an immunoglobulin HCVR that comprises (1) an HCDR1 of SEQ ID NO:111, an HCDR2 of SEQ ID NO:114 and an HCDR3 of SEQ ID NO:115 in combination with (2) an HFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:283, an HFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:277, an HFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:300, and an HFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:274; an immunoglobulin LCVR that comprises (1) an LCDR1 of SEQ ID NO:123, an LCDR2 of SEQ ID NO:124 and an LCDR 3 of SEQ ID NO:125 in combination with (2) an LFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:294, an LFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:295, an LFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:296, and an LFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:276; or both.

In a particular embodiment, a bispecific anti-PD-L1/anti-TIGIT antagonist includes a first targeting domain comprising: an HCVR having the amino acid sequence of SEQ ID NO: 153 and/or an LCVR having the amino acid sequence of SEQ ID NO: 154 in combination with a second targeting domain in the form of an anti-TIGIT scFv comprising an HCVR having the amino acid sequence of SEQ ID NO: 66 and an LCVR having the amino acid sequence of SEQ ID NO: 67. In a more particular embodiment, the scFv in the bispecific anti-PD-L1/anti-TIGIT antagonist comprises a linker joining anti-TIGIT HCVR to the anti-TIGIT LCVR in the second targeting domain, where the linker comprises the amino acid sequence of SEQ ID NO: 191.

In another embodiment, the first targeting domain comprises one or more variable regions from an anti-LAG-3 antibody, and the second targeting domain comprises an anti-TIGIT scFv as described above.

In one embodiment, the anti-LAG-3 targeting domain comprises one or more immunoglobulin heavy chain CDRs selected from SEQ ID NOS: 163-171 and/or one or more immunoglobulin light chain CDRs selected from SEQ ID NOS: 172-178.

In another embodiment, the anti-LAG-3 targeting domain comprises an HCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 180, 182, 184, and 186 and/or an LCVR having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity to an LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOS: 181, 183, 185, and 187.

In another embodiment, the anti-LAG-3 targeting domain includes: an immunoglobulin HCVR comprising (1) an HCDR1 of SEQ ID NO:163, an HCDR2 of SEQ ID NO:164 and an HCDR3 of SEQ ID NO:165 in combination with (2) an HFR1 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:316, an HFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:317, an HFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:318, and an HFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:319; an immunoglobulin LCVR comprising (1) an LCDR1 of SEQ ID NO:172, an LCDR2 of SEQ ID NO:173 and an LCDR 3 of SEQ ID NO:174 in combination with (2) an LFR1 having at least 80%, 85% or 90% identity to the amino acid

sequence of SEQ ID NO:320, an LFR2 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:321, an LFR3 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:322, and an LFR4 having at least 80%, 85% or 90% identity to the amino acid sequence of SEQ ID NO:323; or both.

In another embodiment, the anti-LAG-3 targeting domain comprises an immunoglobulin HCVR having an amino acid sequence that is 90%, 95%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO:180 and/or an immunoglobulin LCVR having an amino acid sequence that is 90%, 95%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO:181.

In a particular embodiment, a bispecific anti-LAG-3/anti-TIGIT antagonist includes a first targeting domain comprising an HCVR having the amino acid sequence of SEQ ID NO:180 and/or an LCVR having the amino acid sequence of SEQ ID NO:181 in combination with an anti-TIGIT scFv comprising an HCVR having the amino acid sequence of SEQ ID NO: 66 and an LCVR having the sequence of SEQ ID NO:67. In a more particular embodiment, the scFv in the bispecific anti-LAG-3/anti-TIGIT antagonist comprises a linker joining anti-TIGIT HCVR to the anti-TIGIT LCVR in the second targeting domain, where the linker comprises the amino acid sequence of SEQ ID NO:189 or SEQ ID NO:191.

In one embodiment, the bispecific anti-LAG-3/anti-TIGIT antagonist includes an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO:192 or 193; an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO:181, or both.

Anti-LAG-3 Antibodies and Antigen Binding Fragments Thereof

In another aspect, the present application provides antibodies, including antigen-binding portions thereof, which specifically bind LAG-3. FIG. 19A shows the heavy chain CDR1, CD2 and CDR3 sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A. FIG. 19B shows the light chain CDR1, CD2 and CDR3 sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A. FIG. 20 shows the VH and VL sequences of anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A.

In one embodiment, an anti-LAG-3 antibody or antigen-binding portion thereof includes: an immunoglobulin heavy chain CDR1 (HCDR1) having at least 80%, at least 85%, or at least 90% sequence identity to an HCDR1 amino acid sequence selected from the group consisting of SEQ ID NOS: 163, 166, and 169; an immunoglobulin heavy chain CDR2 (HCDR2) sequence having at least 80%, at least 85%, or at least 90% sequence identity to an HCDR2 amino acid sequence selected from the group consisting of SEQ ID NOS: 164, 167, and 170; an immunoglobulin heavy chain CDR3 (HCDR3) having at least 80%, at least 85%, or at least 90% sequence identity to an HCDR3 amino acid sequence selected from the group consisting of SEQ ID NOS: 165, 168, and 171; an immunoglobulin light chain CDR1 (LCDR1) having at least 80%, at least 85%, or at least 90% sequence identity to an LCDR1 amino acid sequence selected from the group consisting of SEQ ID NOS: 172, 175, and 177; an immunoglobulin light chain CDR2 (LCDR2) having at least 80%, at least 85%, or at least 90% sequence identity to an LCDR2 amino acid sequence selected from the group consisting of SEQ ID NOS: 173 and 178; and an immunoglobulin light chain CDR3 (LCDR3) having at least 80%, at least 85%, or at least 90% sequence identity to an LCDR3 amino acid sequence selected from the group consisting of SEQ ID NOS: 174, 176 and 179.

In another embodiment, an anti-LAG-3 antibody or antigen-binding portion thereof includes: an immunoglobulin HCDR1 amino acid sequence selected from the group consisting of SEQ ID NOs: 163, 166, and 169; an immunoglobulin HCDR2 amino acid sequence selected from the group consisting of SEQ ID NOs: 164, 167, and 170; an immunoglobulin HCDR3 amino acid sequence selected from the group consisting of SEQ ID NOs: 165, 168, and 171; an immunoglobulin LCDR1 amino acid sequence selected from the group consisting of SEQ ID NOs: 172, 175, and 177; an immunoglobulin LCDR2 amino acid sequence selected from the group consisting of SEQ ID NOs: 173 and 178; and an immunoglobulin LCDR3 amino acid sequence selected from the group consisting of SEQ ID NOs: 174, 176 and 179.

In another embodiment, the anti-LAG-3 antibody or antigen-binding portion thereof includes: an immunoglobulin HCVR having at least 80%, 85%, 90%, 95% or 99% identity to an amino acid sequence selected from the group consisting of SEQ ID NOS: 180, 182, 184, and 186; an immunoglobulin LCVR having at least 80%, 85%, 90%, 95% or 99% identity to an LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 181, 183, 185, and 187; or both.

In another embodiment, the anti-LAG-3 antibody or antigen-binding portion thereof includes: an immunoglobulin HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOS: 180, 182, 184, and 186; an immunoglobulin LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 181, 183, 185, and 187; or both.

In another embodiment, the anti-LAG-3 antibody or antigen-binding portion thereof includes: an immunoglobulin heavy chain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 180; an immunoglobulin light chain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 181; or both.

In a more particular embodiment, the anti-LAG-3 antibody or antigen-binding portion thereof includes: the immunoglobulin heavy chain sequence of SEQ ID NO: 180; the immunoglobulin light chain sequence of SEQ ID NO: 181; or both.

In another aspect, the present application provides one or more nucleic acids encoding any anti-LAG-3 antibody or any antigen-binding portion thereof as described herein.

In another aspect, the present application provides one or more expression vectors comprising one or more nucleic acids encoding any anti-LAG-3 antibody or any antigen-binding portion thereof as described herein.

In another aspect, the present application provides a host cell transformed with the one or more nucleic acids or the one or more expression vectors encoding any anti-LAG-3 antibody or any antigen-binding portion as described herein.

In another aspect, the present application provides a bispecific antitumor antagonist comprising a first targeting domain specifically binding LAG-3; and a second targeting domain specifically binding PD-1, PD-L1 or TIGIT, where the first targeting domain comprises any of the above-described LAG-3-binding portions. Preferably, the anti-LAG-3 bispecific antitumor antagonist includes an immunoglobulin scaffold comprising one or more IgG constant regions, e.g., CH1, CH2, CH3, and/or CL.

In some embodiments, the first targeting domain is positioned at the N-terminal end and the second targeting

domain is positioned at the C-terminal end. In other embodiments, the first targeting domain is positioned at the C-terminal end and the second targeting domain is positioned at the N-terminal end. In yet other embodiments, the second targeting domain is inserted within a loop region of e.g., the CH3 domain.

In one embodiment, a bispecific antitumor antagonist comprises a first targeting domain specifically binding LAG-3, and a second targeting domain specifically binding PD-1, where the first targeting domain comprises any of the anti-LAG-3 binding fragments described above, and where the second targeting domain comprises any of the PD-1 binding fragments described below. For example, in one embodiment, the first targeting domain includes the HCVR amino acid sequence of SEQ ID NO: 180 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 181, and the second targeting domain includes an HCVR having the amino acid sequence of SEQ ID NO: 106 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 107. Alternatively, the second domain may be configured in the form of a PD-1 ECD.

In another embodiment, a bispecific antitumor antagonist includes a first targeting domain specifically binding LAG-3 and a second targeting domain specifically binding PD-L1, where the first targeting domain comprises any of the anti-LAG-3 binding fragments described above, and where the second targeting domain comprises any of the PD-L1 binding fragments described below. For example, in one embodiment, the first targeting domain includes an HCVR having the amino acid sequence of SEQ ID NO: 180 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 181, and the second targeting domain includes an HCVR having the amino acid sequence of SEQ ID NO: 153 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 154.

In another embodiment, a bispecific antitumor antagonist comprises a first targeting domain specifically binding LAG-3 and a second targeting domain specifically binding TIGIT, where the first targeting domain comprises any of the anti-LAG-3 binding fragments described above, and where the second targeting domain comprises any of the TIGIT binding fragments described below. For example, in one embodiment, the first targeting domain includes an HCVR having the amino acid sequence of SEQ ID NO: 180 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 181, and the second targeting domain includes an HCVR having the amino acid sequence of SEQ ID NO: 66 in combination with an LCVR having the amino acid sequence of SEQ ID NO: 67. Alternatively, the second domain may be configured in the form of a TIGIT ECD.

Exemplary immunoglobulin scaffolds include, for example, a complete CH1-CH2-CH3 segment as set forth in SEQ ID NOS: 155-157 and 205-215, or an Fc (hinge-CH2-CH3) comprising the amino acid sequence set forth in any one of SEQ ID NOS: 195-202.

Anti-TIGIT Antibody and Anti-TIGIT Antibody Fragments

In some embodiments, the checkpoint regulator antagonist includes an anti-TIGIT antibody or antigen-binding fragment(s) thereof. FIG. 1 shows CDR sequences of anti-TIGIT mAbs, while FIGS. 2A-2B show several embodiments of anti-TIGIT antibody variable domain sequences for use in the present application.

In one embodiment, the anti-TIGIT antibody or antigen-binding fragment(s) thereof includes: (1) an immunoglobulin HCVR comprising three complementarity determining regions (HCDRs): HCDR1, HCDR2 and HCDR3, where the

HCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 6, 11, 15, 17, 20 and 23, where the HCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 7, 9, 12, 13, 16, 18, 21 and 24, and where the HCDR3 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 5, 8, 10, 14, 19, 22 and 25; and (2) an immunoglobulin LCVR comprising LCDR1, LCDR2 and LCDR3 sequences, where the LCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 26, 29, 31, 33, 35, 39, 42 and 45, wherein the LCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 27, 30, 36, 37, 40, 43 and 46, and where the LCDR3 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 34, 38, 41, 44 and 47; where the antibody or the antigen-binding portion thereof binds specifically to human TIGIT.

In another embodiment, the anti-TIGIT antibody or antigen-binding fragment(s) thereof includes: (1) an immunoglobulin HCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 48, 50, 52, 54, 56, 58, 60, 62, 64, and 66; and (2) an immunoglobulin LCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 49, 51, 53, 55, 57, 59, 61, 63, 65, and 67; where the antibody or the antigen-binding portion thereof binds specifically to human TIGIT.

Anti-PD-1 Antibodies and Antigen-Binding Fragments Thereof

In some embodiments, the checkpoint regulator antagonist includes an anti-PD-1 antibody or antigen-binding fragment(s) thereof. FIG. 3 shows CDR sequences of anti-PD-1 mAbs and FIGS. 4A-4C show several embodiments of anti-PD-1 antibody variable domain sequences for use in the present application.

In one embodiment, the anti-PD-1 antibody or antigen-binding fragment(s) thereof includes: (1) an immunoglobulin HCVR comprising HCDR1, HCDR2 and HCDR3 sequences, where the HCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 68, 71, 74, 76, and 79, where the HCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 69, 72, 77, and 80, and where the HCDR3 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 70, 73, 75, 78, and 81; and (2) an immunoglobulin LCVR comprising LCDR1, LCDR2 and

LCDR3 sequences, where the LCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 82, 85, 88, 89, 90, and 93, where the LCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 83, 86, 91, and 94, and where the LCDR3 has an amino acid sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 84, 87, 92, and 95, where the antibody or the antigen-binding portion thereof binds specifically to human PD-1.

In some embodiments, the anti-PD-1 antibody or antigen-binding fragment(s) thereof include: (1) an immunoglobulin HCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 96, 98, 100, 102, 104, and 106; and (2) an immunoglobulin LCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 97, 99, 101, 103, 105, and 107, where the antibody, or the antigen-binding portion thereof, binds specifically to human PD-1.

Anti-PD-L1 Antibodies and Antigen-Binding Fragment Thereof

In some embodiments, the checkpoint regulator antagonist includes an anti-PD-L1 antibody or antigen-binding fragment(s) thereof. FIG. 5 shows CDR sequences of anti-PD-L1 mAbs and FIGS. 6A-6C show several embodiments of anti-PD-L1 antibody variable domain sequences for use in the present application.

In one embodiment, the PD-L1 antibody or antigen-binding fragment(s) thereof includes: (1) an immunoglobulin HCVR comprising HCDR1, HCDR2 and HCDR3 sequences, where the HCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 108, 111, 117, and 120, where the HCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 109, 112, 114, 116, 118, and 121, where the HCDR3 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 110, 113, 115, 119, and 122; and (2) an immunoglobulin LCVR, wherein the light chain variable region comprises three complementarity determining regions (LCDRs): LCDR1, LCDR2 and LCDR3, wherein the LCDR1 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 123, 126, 130, 133, and 136, wherein the LCDR2 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 124, 127, 131, 134, and 137, and wherein the LCDR3 has an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID

NOS: 125, 128, 129, 132, 135, and 138, wherein the antibody, or the antigen-binding portion thereof, binds specifically to human PD-L1.

In some embodiments, the PD-L1 antibody or antigen-binding fragment(s) thereof include: (1) an immunoglobulin HCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 139, 141, 143, 145, 147, 149, 151, and 153; and (2) an immunoglobulin LCVR having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 140, 142, 144, 146, 148, 150, 152 and 154, where the antibody, or the antigen-binding portion thereof, binds specifically to human PD-L1.

II. Miscellaneous Embodiments

The HCVRs and LCVRs described herein may be linked to an immunoglobulin scaffold. In some embodiments, the immunological scaffold is configured as an IgG1, IgG2 or IgG4. The immunoglobulin scaffold may include CH1-CH2-CH3 regions or it may include a naturally-occurring Fc region or a non-naturally occurring or mutated Fc region, e.g., an effectorless or mostly effectorless Fc (e.g., human IgG2 or IgG4) or, alternatively, an Fc with enhanced binding to one or more activating Fc receptors (FcγRI, FcγRIIa or FcγRIIIa) so as to enhance T_{reg} depletion in the tumor environment. Accordingly, in certain embodiments the anti-TIGIT, anti-PD-1, anti-PD-L1, anti-LAG-3, HCVRs and LCVRs described herein may be linked to an Fc comprising one or more modifications, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity.

In one embodiment, the immunoglobulin scaffold for use in the present application includes a CH1-CH2-CH3 region having an amino acid sequence set forth in SEQ ID NOS: 155-157 and 205-215. In another embodiment, the immunoglobulin scaffold includes or substantially consists of an Fc receptor, such as one having the amino acid sequence set forth in any one of SEQ ID NOS: 195-202.

Furthermore, an antibody described herein may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or it may be modified to alter its glycosylation, to alter one or more functional properties of the antibody. More specifically, in certain embodiments, the antibodies in the present application may include modifications in the Fc region in order to generate an Fc variant with (a) increased or decreased antibody-dependent cell-mediated cytotoxicity (ADCC), (b) increased or decreased complement mediated cytotoxicity (CDC), (c) increased or decreased affinity for Clq and/or (d) increased or decreased affinity for a Fc receptor relative to the parent Fc. Such Fc region variants will generally comprise at least one amino acid modification in the Fc region. Combining amino acid modifications is thought to be particularly desirable. For example, the variant Fc region may include two, three, four, five, etc. substitutions therein, e.g., of the specific Fc region positions identified herein.

For uses where effector function is to be avoided altogether, e.g., when antigen binding alone is sufficient to generate the desired therapeutic benefit, and effector function only leads to (or increases the risk of) undesired side effects, IgG4 antibodies may be used, or antibodies or fragments lacking the Fc region or a substantial portion

thereof can be devised, or the Fc may be mutated to eliminate glycosylation altogether (e.g., N297A). Alternatively, a hybrid construct of human IgG2 (CH1 domain and hinge region) and human IgG4 (CH2 and CH3 domains) may be generated that is devoid of effector function, lacking the ability to bind FcγRs (like IgG2) and activate complement (like IgG4). When using an IgG4 constant domain, it is usually preferable to include the substitution S228P, which mimics the hinge sequence in IgG1 and thereby stabilizes IgG4 molecules, reducing Fab-arm exchange between the therapeutic antibody and endogenous IgG4 in the patient being treated.

In preferred embodiments, the the first and second targeting domains are presented in a humanized immunoglobulin scaffold. Additionally, the IgG scaffold may have a N297A or K447A amino acid substitution.

In certain embodiments, the anti-TIGIT, anti-PD-1, anti-PD-L1, anti-LAG-3, or fragments thereof may be modified to increase its biological half-life. Various approaches may be employed, including e.g., that increase the binding affinity of the Fc region for FcRn. In one embodiment, the antibody is altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022. The numbering of residues in the Fc region is that of the EU index. Sequence variants disclosed herein are provided with reference to the residue number followed by the amino acid that is substituted in place of the naturally occurring amino acid, optionally preceded by the naturally occurring residue at that position. Where multiple amino acids may be present at a given position, e.g., if sequences differ between naturally occurring isotypes, or if multiple mutations may be substituted at the position, they are separated by slashes (e.g., "X/Y/Z").

Exemplary Fc variants that increase binding to FcRn and/or improve pharmacokinetic properties include substitutions at positions 259, 308, and 434, including for example 259I, 308F, 428L, 428M, 434S, 434H, 434F, 434Y, and 434M. Other variants that increase Fc binding to FcRn include: 250E, 250Q, 428L, 428F, 250Q/428L (Hinton et al., 2004, J. Biol. Chem. 279(8): 6213-6216, Hinton et al. 2006 Journal of Immunology 176:346-356), 256A, 272A, 305A, 307A, 31 IA, 312A, 378Q, 380A, 382A, 434A (Shields et al. (2001) J. Biol. Chem., 276(9):6591-6604), 252F, 252Y, 252W, 254T, 256Q, 256E, 256D, 433R, 434F, 434Y, 252Y/254T/256E, 433K/434F/436H (Dall'Acqua et al. (2002) J. Immunol., 169:5171-5180, Dall'Acqua et al. (2006) J. Biol. Chem., 281:23514-23524, and U.S. Pat. No. 8,367,805).

Modification of certain conserved residues in IgG Fc (1253, H310, Q311, H433, N434), such as the N434A variant (Yeung et al. (2009) J. Immunol. 182:7663), have been proposed as a way to increase FcRn affinity, thus increasing the half-life of the antibody in circulation (WO 98/023289). The combination Fc variant comprising M428L and N434S has been shown to increase FcRn binding and increase serum half-life up to five-fold (Zalevsky et al. (2010) Nat. Biotechnol. 28:157). The combination Fc variant comprising T307A, E380A and N434A modifications also extends half-life of IgG1 antibodies (Petkova et al. (2006) Int. Immunol. 18:1759). In addition, combination Fc variants comprising M252Y-M428L, M428L-N434H, M428L-N434F, M428L-N434Y, M428L-N434A, M428L-N434M, and M428L-N434S variants have also been shown to extend half-life (U.S. 2006/173170). Further, a combination Fc variant comprising M252Y, S254T and T256E was

reported to increase half-life-nearly 4-fold. Dall'Acqua et al. (2006) J. Biol. Chem. 281:23514.

The bispecific antitumor antagonists of the present application may be constructed with an IgG backbone. More specifically, any of the bispecific antagonists of the present application may be constructed with an IgG1 or IgG4 backbone. Use of an IgG1 backbone is preferable for cancer treatment where a target is present on antigen presenting cells that can mediate antibody-dependent cell-mediated cytotoxicity (ADCC). Use of an IgG4 backbone allows targeting of antigen where antigen binding alone is sufficient to generate the desired therapeutic benefits. IgG4-based antagonists preclude undesirable effector functions associated with e.g., IgG1 antibodies, including FcγR binding and complement activation.

Homodimers and Heterodimers

One of the challenges for efficiently producing bispecific antibody preparations concerns mispairing of heavy and light chains, when co-expressing chains of different binding specificities. Table 1 lists several amino acid substitution options for overcoming mispairing between heavy chains of different binding specificities, which “enforce” or preferentially promote correct association between desired heavy chains. Any approach to prevent or reduce mispairing between heavy chains may be used to make the bispecific antitumor antagonists according to the present disclosure.

The “knobs-into-hole” (KiH) approach relies on modifications of the interface between the two CH3 domains where most interactions occur. Typically, a bulky residue is introduced into the CH3 domain of one antibody heavy chain and acts similarly to a key. In the other heavy chain, a “hole” is formed that is able to accommodate this bulky residue, mimicking a lock. The resulting heterodimeric Fc-part can be further stabilized by artificial disulfide bridges.

An alternative approach is based on charged residues with ionic interactions or steric complementarity. This includes altering the charge polarity in the CH3 interface so that co-expression of electrostatically matched Fc domains support favorable attractive interactions and heterodimer formation while retaining the hydrophobic core, whereas unfavorable repulsive charge interactions suppress homodimerization. See Table 1. The amino acid numbering in Table 1 follows the Kabat numbering scheme and can be applied to heavy chain amino acid sequences of the antibodies described herein.

In some embodiments, an immunological scaffold may be substituted with another dimer structure containing, for example, leucine zipper (LZ) domains. A leucine zipper is a common three-dimensional structural motif in proteins, typically as part of a DNA-binding domain in various transcription factors. A single LZ typically contains 4-5 leucine residues at approximately 7-residue intervals, which forms an amphipathic alpha helix with a hydrophobic region running along one side. In a particular embodiment, a heterodimeric protein scaffold comprises a LZ from the c-jun transcription factor associated with a LZ from the c-fos transcription factor. Although c-jun is known to form jun-jun homodimers and c-fos does not form homodimers, the formation of jun-fos heterodimers is greatly favored over jun-jun homodimers.

A leucine zipper domain may be incorporated in place of CH2-CH3 sequences in the protein scaffold or it may be placed at the carboxy terminal end of the two heavy chains in the bispecific antitumor antagonist. In the case of the latter, a furin cleavage site may be introduced between the carboxy terminal end of CH3 and the amino terminal end of the leucine zipper. This can facilitate furin-mediated cleav-

age of the leucine zipper following the heterodimerization step when co-expressing the heavy and light chains of the bispecific antitumor antagonist in an appropriate mammalian cell expression system (see Wranik et al., J. Biol. Chem., 287(5):43331-43339, 2012).

TABLE 1

Type	HC1	HC2
Knobs-into-holes	Y349C, T366S, L368A, Y407V	S354C, T366W
Ionic, electrostatic	S183E, E356K, E357K, D399K	S183K, K370E, K409D, K439E
Ionic, electrostatic	K392D, K409D	E356K, D399K
HA-TF substitutions	S364H, F405A	Y349T, T394F
HF-TA substitutions	S364H, T394F	Y349T, F405A
Leucine zipper heterodimer	human c-Jun leucine zipper	human c-fos leucine zipper

The amino acid numbering in Table 1 follows the Kabat numbering scheme and can be applied to heavy chain amino acid sequences of the antibodies described herein. The mutations described in Table 1 may be applied to the sequence (published or otherwise) of any immunoglobulin IgG1 heavy chain, as well as other immunoglobulin classes, and subclasses (or isotypes) therein.

When co-expressing heavy and light chains of monospecific, bispecific antibodies, a light chain of one binding specificity can also mispair with a heavy chain of a different binding specificity. Therefore, in certain embodiments, portions of the heavy chain, light chain or both may be modified relative to the “wild-type” antibody chains from which they are derived to prevent or reduce mispairing of both heavy chain constant regions to one another, as well mispairing of light chain constant regions to their heavy chain counterparts.

The light chain mispairing problem can be addressed in several ways. In some embodiments, sterically complementary mutations and/or disulfide bridges may be incorporated into the two VL/VH interfaces. In other embodiments, mutations can be incorporated based on ionic or electrostatic interactions. In some embodiments, light chain mispairing may be prevented or reduced by employing a first arm with an S183E mutation in the CH1 domain of the heavy chain and an S176K mutation in the CL domain of the light chain. A second arm may include an S183K mutation in the in the CH1 domain of the heavy chain and an S176E mutation in the CL domain of the light chain. In other embodiments, a “CrossMab” approach is employed, where one arm in the bispecific antitumor antagonist (e.g., Fab) is left untouched, but in the other arm containing the other binding specificity, one or more domains in the light chain are swapped with one or more domains in the heavy chain at the heavy chain:light chain interface.

Methods, immunoglobulin domain sequences, including specific mutations for preventing mispairing of heavy and light chains as disclosed above are further described in U.S. Patent Application Publication Nos. 2014/0243505, 2013/0022601.

Conjugates

In certain embodiments, the antitumor antagonists of the present application are chemically conjugated to one or more peptides and/or small molecule drugs. The peptides or small molecule drug can be the same or different. The peptides or small molecule drugs can be attached, for example to reduced SH groups and/or to carbohydrate side chains. Methods for making covalent or non-covalent con-

jugates of peptides or small molecule drugs with antibodies are known in the art and any such known method may be utilized.

In some embodiments the peptide or small molecule drug is attached to the hinge region of a reduced antibody component via disulfide bond formation. Alternatively, such agents can be attached using a heterobifunctional cross-linkers, such as N-succinyl 3-(2-pyridyldithio)propionate (SPDP). General techniques for such conjugation are well-known in the art. In some embodiments, the peptide or small molecule drug is conjugated via a carbohydrate moiety in the Fc region of the antibody. The carbohydrate group can be used to increase the loading of the same agent that is bound to a thiol group, or the carbohydrate moiety can be used to bind a different therapeutic or diagnostic agent. Methods for conjugating peptide inhibitors or small molecule drugs to antibodies via antibody carbohydrate moieties are well-known to those of skill in the art. For example, in one embodiment, the method involves reacting an antibody component having an oxidized carbohydrate portion with a carrier polymer that has at least one free amine function. This reaction results in an initial Schiff base (imine) linkage, which can be stabilized by reduction to a secondary amine to form the final conjugate. Exemplary methods for conjugating small molecule drugs and peptides to antibodies are described in U.S. Patent Application Publication No. 2014/0356385.

Preferably, the antitumor antagonists in the present disclosure retain certain desirable characteristics and pharmacokinetic properties of antibodies, including a desirable in vitro and in vivo stability (e.g., lone half-life and shelf-life stability), efficient delivery into desired target cells, increased affinity for binding partners, desirable antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, and reduced renal clearance or excretion. Accordingly, careful attention to size and need for particular constant region effector functions may be considered in the design of the antitumor antagonists.

The anti-TIGIT, anti-PD-1 and anti-PD-L1 inhibitors, including monospecific, bispecific antitumor antagonists therefrom, may range in size from 50 kD to 300 kD, from 50 kD to 250 kD, from 60 kD to 250 kD, from 80 kDa to 250 kD, from 100 kD to 250 kD, from 125 kD to 250 kD, from 150 kD to 250 kD, from 60 kD to 225 kD, from 75 kD to 225 kD, from 100 kD to 225 kD, from 125 kD to 225 kD, from 150 kD to 225 kD, from 60 kD to 200 kD, from 75 kD to 200 kD, from 100 kD to 125 kD to 200 kD, from 150 kD to 200 kD, from 60 kD to 150 kD, from 75 kD to 150 kD, from 100 kD to 150 kD, from 60 kD to 125 kD, from 75 kD to 125 kD, from 75 kD to 100 kD, or any range encompassed by any combination of whole numbers listed in the above cited ranges or any ranges specified by any combination of whole numbers between any of the above cited ranges.

Kits

The present application further provides a kit comprising any one or more of the checkpoint regulator antagonist or antitumor antagonist of the present application. In some embodiments, the kit further contains additional components, including syringes and needles for administration, as well as reagents, including secondary antibodies for detection, and additional human antibodies described herein for use in combination therapies therewith. A kit typically includes a label and/or instructions indicating the intended use of the contents of the kit. The label or instruction may

include any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

III. Methods of Using the Antitumor Antagonists

The antitumor antagonists of the present application have numerous in vitro and in vivo utilities including, for example, enhancement of immune responses and treatment of cancers, infectious diseases or autoimmune diseases.

In certain embodiments, the present application provides a method for treating: a cell proliferative disorder; a method of reducing or depleting regulatory T cells in a tumor; a method for treating a microbial infection; or a method for treating an immunological disorder, where the method comprises administering to a subject in need thereof an effective amount of an antitumor antagonist according to the present application.

In some embodiments, the antitumor antagonists of the present application are administered to cells in culture, in vitro or ex vivo, or to human subjects, e.g., in vivo, to enhance immunity in a variety of diseases. Accordingly, provided herein are methods of modifying an immune response in a subject comprising administering to the subject an antibody or antigen-binding fragment thereof as described herein such that the immune response in the subject is enhanced, stimulated or up-regulated. Preferred subjects include human patients in whom enhancement of an immune response would be desirable. The methods are particularly suitable for treating human patients having a disorder that can be treated by augmenting an immune response (e.g., the T-cell mediated immune response). The methods are particularly suitable for treatment of cancer or chronic infections in vivo. For example, the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 compositions may be administered together with an antigen of interest or the antigen may already be present in the subject to be treated (e.g., a tumor-bearing or virus-bearing subject) to enhance antigen-specific immunity. When anti-TIGIT antibodies are administered together with another agent, the two can be administered separately or simultaneously.

In some embodiments, the checkpoint regulator antagonist used in the above-described method is an anti-TIGIT, anti-PD-1, anti-PD-L1 antibody, anti-LAG-3 antibody, a fragment thereof, or combination thereof. In some embodiments, the checkpoint regulator antagonist is a monospecific or bispecific antibody.

In some embodiments, the checkpoint regulator antagonist or antitumor antagonist is in the form of an antibody or antibody fragment. In some embodiments, the antibodies described herein are human or humanized antibodies.

Also encompassed are methods for detecting and/or measuring the presence of human TIGIT, human PD-1, human PD-L1 or human LAG3 in a sample comprising contacting the sample, and a control sample, with a human monoclonal antibody thereof, or an antigen binding fragment thereof, which specifically binds to human TIGIT, human PD-1 or human PD-L1 under conditions that allow for formation of a complex between the antibody or fragment thereof and human TIGIT, human PD-1 or human PD-L1. The formation of a complex is then detected, wherein a difference in complex formation between the sample compared to the control sample is indicative the presence of human TIGIT antigen in the sample.

Given the ability of anti-TIGIT, anti-PD-1, anti-PD-L1 and anti-LAG-3 antibodies to block inhibition or co-inhibition of T cell responses, e.g., antigen-specific T cell responses, provided herein are in vitro and in vivo methods

of using the antibodies described herein to stimulate, enhance or upregulate antigen-specific T cell responses, e.g., anti-tumor T cell responses. In certain embodiments, CD3 stimulation is also provided (e.g., by co-incubation with a cell expressing membrane CD3), which stimulation can be provided at the same time, before, or after treatment with an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody. For example, the present application provides a method of enhancing an antigen-specific T cell response comprising contacting a T cell with an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody described herein, and optionally with CD3, such that an antigen-specific T cell response is enhanced, e.g., by removal of a TIGIT, PD-1, PD-L1 or LAG-3 mediated inhibitory effect. Any suitable indicator of an antigen-specific T cell response can be used to measure the antigen-specific T cell response. Non-limiting examples of such suitable indicators include increased T cell proliferation in the presence of the antibody and/or increase cytokine production in the presence of the antibody. In a preferred embodiment, interleukin-2 and/or interferon- γ production by the antigen-specific T cell is enhanced.

Further encompassed are methods for enhancing an immune response (e.g., an antigen-specific T cell response) in a subject comprising administering an anti-TIGIT antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-LAG-3 antibody, or a bispecific antitumor antagonist described herein to the subject such that an immune response (e.g., an antigen-specific T cell response) in the subject is enhanced. In a preferred embodiment, the subject is a tumor-bearing subject and an immune response against the tumor is enhanced. A tumor may be a solid tumor or a liquid tumor, e.g., a hematological malignancy. In certain embodiments, a tumor is an immunogenic tumor. In other embodiments, a tumor is non-immunogenic. In certain embodiments, a tumor is PD-L1 positive. In other embodiments a tumor is PD-L1 negative. A subject may also be a virus-bearing subject in which an immune response against the virus is enhanced as a consequence of administering an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, monospecific antitumor antagonist or bispecific antitumor antagonist, as described herein.

In one embodiment, a method for inhibiting the growth of tumor cells in a subject comprises administering to the subject an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist described herein such that growth of the tumor is inhibited in the subject. Also provided are methods of treating chronic viral infection in a subject comprising administering to the subject an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist as described herein such that the chronic viral infection is treated in the subject.

Also encompassed herein are methods for depleting T_{reg} cells from the tumor microenvironment of a subject with a tumor, e.g., cancerous tumor, comprising administering to the subject a therapeutically effective amount of an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, or bispecific antitumor antagonist described herein that comprises an Fc that stimulates depletion of T_{reg} cells in the tumor microenvironment. An Fc may, e.g., be an Fc with effector function or enhanced effector function, such as binding or having enhanced binding to one or more activating Fc receptors.

In a preferred embodiment, T_{reg} depletion occurs without significant depletion or inhibition of T_{eff} in the tumor microenvironment, and without significant depletion or inhi-

bition of T_{eff} cells and T_{reg} cells outside of the tumor microenvironment. In certain embodiments, the subject has higher levels of TIGIT on T_{reg} cells than on T_{eff} cells, e.g., in the tumor microenvironment. In certain embodiments, anti-TIGIT antibodies or antagonists may deplete T_{regs} in tumors and/or T_{regs} in tumor infiltrating lymphocytes (TILs). For example, in the CT26 tumor model, an anti-mouse TIGIT antibody formatted as a mouse IgG2a (which exhibits effector function) partially depleted both T_{reg} and CD8⁺ T cells, but did not deplete CD4⁺ T cells. An effectorless counterpart anti-TIGIT antibody, formatted as a mouse IgG1 D265A, did not deplete T cells.

When considering whether or not to employ Fc effector function or an effectorless anti-TIGIT antibody, due consideration must be given to the tradeoff between depletion of T_{regs} , which may enhance anti-tumor immune response, and depletion of CD8⁺ T cells, which would eliminate some of the cells needed to actually kill tumor cells. Although depletion of T_{regs} might be expected to enhance anti-tumor activity, recent studies have demonstrated that ligation of TIGIT on TIGIT T_{regs} promotes T_{reg} cell-mediated suppression of T_{eff} cell proliferation (Joller et al. (2014) Immunity 40:569), suggesting that blocking of TIGIT signaling (e.g., using an antagonist anti-TIGIT antibody of the present invention) might also enhance anti-tumor activity. Accordingly, it may be most efficacious to use an antagonist anti-TIGIT antibody lacking effector function, which: i) blocks TIGIT signaling in T_{regs} thus reducing their immunosuppressive activity; ii) activates anti-tumor CD8⁺ T cells by blocking TIGIT's inhibitory effects, while at the same time avoiding their effector-function-mediated depletion; and iii) enhances DNAM-mediated activation by allowing DNAM to bind to PVR (CD155, the TIGIT ligand) that would otherwise have been bound by TIGIT (and by reducing direct TIGIT-DNAM interactions) (Johnston et al. (2014) Cancer Cell 26:923). The same is applicable to use of anti-PD-1 antibodies, anti-PD-L1 antibodies or bispecific antitumor antagonists.

In certain embodiments, an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist described herein is given to a subject as an adjunctive therapy. Treatment of cancer patient with an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist according to the present application may lead to a long-term durable response relative to the current standard of care; long term survival of at least 1, 2, 3, 4, 5, 10 or more years, recurrence free survival of at least 1, 2, 3, 4, 5, or 10 or more years. In certain embodiments, treatment of a cancer patient with an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist prevents recurrence of cancer or delays recurrence of cancer by, e.g., 1, 2, 3, 4, 5, or 10 or more years. An anti-TIGIT, anti-PD-1, anti-PD-L1 and/or anti-LAG-3 treatment can be used as a primary or secondary line of treatment.

In certain preferred embodiments, the subject has a cell proliferative disease or cancer. Blocking of PVR/Nectin-2 signaling through TIGIT by anti-TIGIT antibodies can enhance the immune response to cancerous cells in the patient. Similarly, blocking of Provided herein are methods for treating a subject having cancer, comprising administering to the subject an anti-TIGIT, anti-PD-1, anti-PD-L1, anti-LAG-3 or bispecific antitumor antagonist thereof as described herein, such that the subject is treated, e.g., such that growth of cancerous tumors is inhibited or reduced and/or that the tumors regress. An anti-TIGIT anti-PD-1,

anti-PD-L1, anti-LAG-3 or bispecific antitumor antagonist thereof as described herein can be used alone to inhibit the growth of cancerous tumors. Alternatively, any of these antitumor antagonists can be used in conjunction with another agent, e.g., other anti-cancer targets, immunogenic agents, standard cancer treatments, or other antibodies, as described below.

Accordingly, provided herein are methods of treating cancer, e.g., by inhibiting growth of tumor cells, in a subject, comprising administering to the subject a therapeutically effective amount of an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antagonist, or a bispecific antitumor antagonist, as described herein. Preferably, the antibody is a human anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody comprising the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 HCVRs and LCVR described herein, or it may be a chimeric, humanized, or non-human anti-hu TIGIT, anti-hu PD-1, anti-PD-L1 antibody or anti-LAG-3 antibody, e.g., a chimeric, humanized, or non-human anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody that competes for binding with, or binds to the same epitope as, at least one of the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibodies described herein.

Cancers whose growth may be inhibited using the antibodies of the invention include cancers typically responsive to immunotherapy. Non-limiting examples of cancers for treatment include squamous cell carcinoma, small-cell lung cancer, non-small cell lung cancer, squamous non-small cell lung cancer (NSCLC), non NSCLC, glioma, gastrointestinal cancer, renal cancer (e.g. clear cell carcinoma), ovarian cancer, liver cancer, colorectal cancer, endometrial cancer, kidney cancer (e.g., renal cell carcinoma (RCC)), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), thyroid cancer, neuroblastoma, pancreatic cancer, glioblastoma (glioblastoma multiforme), cervical cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer (or carcinoma), gastric cancer, germ cell tumor, pediatric sarcoma, sinonasal natural killer, melanoma (e.g., metastatic malignant melanoma, such as cutaneous or intraocular malignant melanoma), bone cancer, skin cancer, uterine cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally-induced cancers including those induced by asbestos, virus-related cancers (e.g., human papilloma virus (HPV)-related tumor), and hematologic malignancies derived from either of the two major blood cell lineages, i.e., the myeloid cell line (which produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells) or lymphoid cell line (which produces B, T, NK and plasma cells), such as all types of leukemias, lymphomas, and myelomas, e.g., acute, chronic, lymphocytic and/or myelogenous leukemias, such as acute leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CIVIL), undifferentiated AML (MO), myeloblastic leukemia (M1), myeloblastic leukemia (M2; with cell maturation), promy-

elocytic leukemia (M3 or M3 variant [M3V]), myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]), monocytic leukemia (M5), erythroleukemia (M6), megakaryoblastic leukemia (M7), isolated granulocytic sarcoma, and chloroma; lymphomas, such as Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NEIL), B-cell lymphomas, T-cell lymphomas, lymphoplasmacytoid lymphoma, monocytoid B-cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, anaplastic (e.g., Ki 1+) large-cell lymphoma, adult T-cell lymphoma/leukemia, mantle cell lymphoma, angio immunoblastic T-cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, primary mediastinal B-cell lymphoma, precursor T-lymphoblastic lymphoma, T-lymphoblastic; and lymphoma/leukemia (T-Lbly/T-ALL), peripheral T-cell lymphoma, lymphoblastic lymphoma, post-transplantation lymphoproliferative disorder, true histiocytic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, lymphoblastic lymphoma (LBL), hematopoietic tumors of lymphoid lineage, acute lymphoblastic leukemia, diffuse large B-cell lymphoma, Burkitt's lymphoma, follicular lymphoma, diffuse histiocytic lymphoma (DHL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, cutaneous T-cell lymphoma (CTLC) (also called mycosis fungoides or Sezary syndrome), and lymphoplasmacytoid lymphoma (LPL) with Waldenstrom's macroglobulinemia; myelomas, such as IgG myeloma, light chain myeloma, nonsecretory myeloma, smoldering myeloma (also called indolent myeloma), solitary plasmacytoma, and multiple myelomas, chronic lymphocytic leukemia (CLL), hairy cell lymphoma; hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; seminoma, teratocarcinoma, tumors of the central and peripheral nervous, including astrocytoma, schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoacanthoma, seminoma, thyroid follicular cancer and teratocarcinoma, hematopoietic tumors of lymphoid lineage, for example T-cell and B-cell tumors, including but not limited to T-cell disorders such as T-prolymphocytic leukemia (T-PLL), including of the small cell and cerebriform cell type; large granular lymphocyte leukemia (LGL) preferably of the T-cell type; a/d T-NHL hepatosplenic lymphoma; peripheral/post-thymic T cell lymphoma (pleomorphic and immunoblastic subtypes); angiocentric (nasal) T-cell lymphoma; cancer of the head or neck, renal cancer, rectal cancer, cancer of the thyroid gland; acute myeloid lymphoma, as well as any combinations of said cancers. The methods described herein may also be used for treatment of metastatic cancers, refractory cancers (e.g., cancers refractory to previous immunotherapy, e.g., with a blocking CTLA-4 or PD-1 antibody), and recurrent cancers.

An anti-TIGIT, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist can be administered alone, in combination with another antitumor antagonist, or concurrently with another antitumor antagonist. An anti-TIGIT, anti-PD-1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist can also be administered in combination, or concurrently with, an immunogenic agent, such as cancerous cells, tumor vaccines, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells transfected with genes encoding immune stimulating cytokines, in a cancer vaccine strategy (He et al. (2004) J. Immunol. 173:4919-28), or an oncolytic virus.

Many experimental strategies for vaccination against tumors have been devised. In one of these strategies, a vaccine is prepared using autologous or allogeneic tumor cells. Some of these cellular vaccines have been shown to be most effective when the tumor cells are transduced to express GM-CSF. GM-CSF has been shown to be a potent activator of antigen presentation for tumor vaccination (Dranoff et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90: 3539-43). Cancer vaccines have been shown to enhance effector T-cell infiltration into the tumors in preclinical models. The major types of cancer vaccines include peptide vaccines, vector-based antigen specific vaccines, whole-cell vaccines, and dendritic cell vaccines. All vaccine-based therapies are designed to deliver either single or multiple antigenic epitopes or antigens from the whole cells to the patients and induce tumor-specific effector T cells. Thus, a vaccine-based therapy may be the most efficient way to induce T-cell infiltration into the tumor.

The study of gene expression and large scale gene expression patterns in various tumors has led to the definition of so called tumor specific antigens (Rosenberg, S A (1999) *Immunity* 10: 281-7). In many cases, these tumor specific antigens are differentiation antigens expressed in the tumors and in the cell from which the tumor arose, for example melanocyte antigens gp100, MAGE antigens, and Trp-2. More importantly, many of these antigens can be shown to be the targets of tumor specific T cells found in the host.

TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition may be used in conjunction with a collection of recombinant proteins and/or peptides expressed in a tumor in order to generate an immune response to these proteins. Such proteins may be viewed by the immune system as self-antigens and are therefore tolerant to them. The tumor antigen can include the protein telomerase, which is required for the synthesis of telomeres of chromosomes and which is expressed in more than 85% of human cancers and in only a limited number of somatic tissues (Kim et al. (1994) *Science* 266: 2011-2013). Tumor antigens can also be "neo-antigens" expressed in cancer cells because of somatic mutations that alter protein sequence or create fusion proteins between two unrelated sequences (i.e., bcr-abl in the Philadelphia chromosome), or idiotype from B cell tumors.

Non-limiting examples of tumor vaccines include sipuleucel-T (Provenge®), an FDA-approved tumor vaccine for metastatic prostate cancer; tumor cells transfected to express the cytokine granulocyte macrophage colony-stimulating factor (GM-CSF), such as the whole cell GM-CSF-secreting irradiated, allogeneic pancreatic cancer vaccine (GVAX; Johns Hopkins); a multi-peptide vaccine consisting of immunogenic peptides derived from breast cancer antigens, neu, legumain, and β -catenin, which prolonged the vaccine-induced progression-free survival of breast tumor-bearing mice when administered in combination with anti-PD-1 antibody (Karyampudi L. et al. (2014) *Cancer Res* 74:2974-2985); peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or. Other tumor vaccines include proteins from viruses implicated in human cancers such as human papilloma viruses (HPV) (e.g., Gardasil®, Gardasil 9®, and Cervarix®; hepatitis B virus (e.g., Engerix-B and Recombivax HB); hepatitis C virus (HCV), Kaposi's sarcoma associated herpes sarcoma virus (KSHV). Another form of tumor specific antigen that can be used in conjunction with TIGIT inhibition is purified heat shock proteins (HSP) isolated from the tumor tissue itself. These heat shock proteins contain fragments of proteins from the tumor cells and these HSPs are highly efficient at delivery to antigen

presenting cells for eliciting tumor immunity. Talimogene laherparepvec (T-VEC, or Imlygic®) is an FDA-approved oncolytic virus for the treatment of some patients with metastatic melanoma that cannot be surgically removed.

Dendritic cells (DC) are potent antigen presenting cells that can be used to prime antigen-specific responses. DC's can be produced ex vivo and loaded with various protein and peptide antigens, as well as tumor cell extracts (Nestle et al. (1998) *Nature Medicine* 4: 328-332). DCs can also be transduced by genetic means to express these tumor antigens as well. DCs have also been fused directly to tumor cells for the purposes of immunization (Kugler et al. (2000) *Nature Medicine* 6:332-336). As a method of vaccination, DC immunization may be effectively combined with TIGIT blocking to activate (unleash) more potent anti-tumor responses.

TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition can also be combined with standard cancer treatments (e.g., surgery, radiation, and chemotherapy). In particular, TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition can be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of chemotherapeutic reagent administered (Mokyr et al. (1998) *Cancer Research* 58: 5301-5304). An example of such a combination is an anti-tumor antagonist in combination with decarbazine for the treatment of melanoma. Another example of such a combination is a checkpoint regulator antagonist or antitumor antagonist in combination with interleukin-2 (IL-2) for the treatment of melanoma. For example, the scientific rationale behind the combined use of TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition and chemotherapy to promote cell death is a consequence of the cytotoxic action of most chemotherapeutic compounds, should result in increased levels of tumor antigen in the antigen presentation pathway. Other combination therapies that may result in synergy with TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition through cell death are radiation, surgery, and hormone deprivation. Each of these protocols creates a source of tumor antigen in the host. Angiogenesis inhibitors can also be combined with TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition. Inhibition of angiogenesis leads to tumor cell death, which may feed tumor antigen into host antigen presentation pathways.

The anti-TIGIT antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-LAG-3 antibodies, and bispecific antitumor antagonists described herein may also be used in combination with bispecific antibodies that target Fc α or Fc γ receptor-expressing effectors cells to tumor cells (see, e.g., U.S. Pat. Nos. 5,922,845 and 5,837,243). Bispecific antibodies can be used to target two separate antigens. For example anti-Fc receptor/antitumor antigen (e.g., Her-2/neu) bispecific antibodies have been used to target macrophages to sites of tumor. This targeting may more effectively activate tumor specific responses. The T cell arm of these responses would be augmented by the inhibition of TIGIT, PD-1, PD-L1 and/or LAG-3. Alternatively, antigen may be delivered directly to DCs by the use of bispecific antibodies that bind to tumor antigen and a dendritic cell specific cell surface marker.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of immunosuppressive proteins expressed by the tumors. These include among others TGF- β , IL-10, and Fas ligand. Antibodies to each of these entities can be used in combination with the antitumor antagonists described herein to counteract the effects of the immunosuppressive agent and favor tumor immune responses by the host.

Other antibodies that activate host immune responsiveness can be used in combination with the antitumor antagonists described herein. These include molecules on the surface of dendritic cells that activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity (Ridge et al. (1998) Nature 393: 474-478) and can be used in conjunction with anti-TIGIT antibodies. Activating antibodies to T cell costimulatory molecules, such as OX-40 (Weinberg et al. (2000) Immunol 164: 2160-2169), CD137/4-1BB (Melero et al. (1997) Nature Medicine 3: 682-685 (1997), and ICOS (Hutloff et al. (1999) Nature 397: 262-266) may also provide for increased levels of T cell activation. In addition, inhibitors of other immune checkpoint regulators may also be used in conjunction with other antitumor antagonists described herein, as further described below.

Bone marrow transplantation is currently being used to treat a variety of tumors of hematopoietic origin. While graft versus host disease is a consequence of this treatment, TIGIT inhibition may be used to increase the effectiveness of the donor engrafted tumor specific T cells by reducing graft vs. tumor responses.

Ex vivo activation and expansion of antigen specific T cells and adoptive transfer of these cells into recipients in order to stimulate antigen-specific T cells against cancers or viral infections in the presence of anti-TIGIT antibodies can increase the frequency and activity of the adoptively transferred T cells.

There are also several experimental treatment protocols that involve ex vivo activation and expansion of antigen specific T cells and adoptive transfer of these cells into recipients in order to stimulate antigen-specific T cells against tumor (Greenberg & Riddell (1999) Science 285: 546-51). These methods can also be used to activate T cell responses to infectious agents such as CMV. Ex vivo activation in the presence of anti-TIGIT antibodies can increase the frequency and activity of the adoptively transferred T cells.

In certain embodiments, an antitumor antagonist described herein may be administered to a subject with an infectious disease, especially chronic infections. In this case, similar to its application to cancer, antibody-mediated TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition can be used alone, or as an adjuvant, in combination with vaccines, to enhance immune responsiveness to pathogens, toxins, and self-antigens. Exemplary pathogens for which this therapeutic approach can be applied include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, and Pseudomonas aeruginosa. TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition is particularly useful against established infections by agents such as HIV that present novel or altered antigens over the course of the infections. Administration of the anti-TIGIT antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies or bispecific antitumor antagonists can allow for recognition of these antigens as foreign so as to provoke an appropriate T cell response.

Other pathogenic viruses causing infections treatable by the methods described herein include HIV, hepatitis (A, B, or C), herpesvirus infections (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), and infections caused by an adenovirus, influenza virus, flavivirus, echoviruses, rhinoviruses, coxsackie viruses, coronaviruses, respiratory syncytial viruses, mumps viruses, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum

virus, poliovirus, rabies virus, JC virus, arboviral encephalitis virus, or combination thereof.

Exemplary pathogenic bacteria or diseases caused therefrom which may be treatable by the methods described herein include *Chlamydia*, *Rickettsia*, *Mycobacteria*, *Staphylococci*, *Streptococci*, *Pneumococci*, *Meningococci* and *Gonococci*, *Klebsiella*, *Proteus*, *Serratia*, *Pseudomonas*, *Legionella*, *Diphtheria*, *Salmonella*, *Bacilli*, *Cholera*, *Leptospirosis* tetanus, botulism, anthrax, plague, and Lyme disease.

Exemplary pathogenic fungi causing infections treatable by the methods described herein include *Candida* (e.g., *albicans*, *krusei*, *glabrata*, *tropicalis*, etc.), *Cryptococcus neoformans*, *Aspergillus* (e.g., *fumigatus*, *niger*, etc.), *Mucorales* (e.g., *mucor*, *absidia*, *rhizopus*), *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis* and *Histoplasma capsulatum*.

Exemplary pathogenic parasites causing infections treatable by the methods described herein include *Entamoeba histolytica*, *Balantidium coli*, *Naegleria fowleri*, *Acanthamoeba* sp., *Giardia* *Zambia*, *Cryptosporidium* sp., *Pneumocystis carinii*, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondii*, *Nippostrongylus brasiliensis*.

In all of the above methods, TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition can be combined with other forms of immunotherapy, such as cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), or bispecific antibody therapy using two different binding specificities to provide enhanced presentation of tumor antigens.

Anti-TIGIT antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-LAG-3 antibodies and bispecific antitumor antagonists described herein can be used to enhance antigen-specific immune responses by co-administration of one or more of any of these antibodies with an antigen of interest (e.g., a vaccine). Accordingly, provided herein are methods of enhancing an immune response to an antigen in a subject, comprising administering to the subject: (i) the antigen; and (ii) an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antitumor antagonist, or combination thereof, such that an immune response to the antigen in the subject is enhanced. The antigen can be, for example, a tumor antigen, a viral antigen, a bacterial antigen or an antigen from a pathogen. Non-limiting examples of such antigens include those discussed in the sections above, such as the tumor antigens (or tumor vaccines) discussed above, or antigens from the viruses, bacteria or other pathogens described above.

In certain embodiments, a peptide or fusion protein comprising the epitope to which an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, LAG-3 antibody or bispecific antitumor antagonist binds may be used as a vaccine instead of, or in addition to, the antitumor antagonist (s).

Suitable routes of administering the antibody compositions (e.g., human monoclonal antibodies, multi-specific antibodies or antagonists and immunoconjugates) described herein in vivo and in vitro are well known in the art and can be selected by those of ordinary skill. For example, the antibody compositions can be administered by injection (e.g., intravenous or subcutaneous). Suitable dosages of the molecules used will depend on the age and weight of the subject and the concentration and/or formulation of the antibody composition.

Combination Therapies

In another aspect, the present application provides combination therapies for enhancing an antigen-specific T cell

response in a subject. In one embodiment, the method includes contacting a T cell with an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, antibody fragment thereof or bispecific antitumor antagonist in combination with a second antibody, antibody fragment, antagonist or drug such that an antigen-specific T cell response or apoptotic pathway is enhanced. For example, in some embodiments, the first antibody or antibody fragment specifically binds TIGIT and the second antibody or antibody fragment specifically binds to PD-1, PD-L1 or LAG-3.

In a related aspect, a method of reducing or depleting regulatory T cells in a tumor of a subject in need thereof includes administering an effective amount of an antibody or antibody fragment in combination with a second antibody, antibody fragment, antagonist or drug such that the number of regulatory T cells in the subject is reduced.

In some embodiments, the subject has a cell proliferative disease or cancer as described herein.

In other embodiments, the subject has a chronic viral infection, inflammatory disease or autoimmune disease as described herein.

The provision of two distinct signals to T-cells is a widely accepted model for lymphocyte activation of resting T lymphocytes by antigen-presenting cells (APCs). This model further provides for the discrimination of self from non-self and immune tolerance. The primary signal, or antigen specific signal, is transduced through the T-cell receptor (TCR) following recognition of foreign antigen peptide presented in the context of the major histocompatibility-complex (MHC). The second or co-stimulatory signal is delivered to T-cells by co-stimulatory molecules expressed on antigen-presenting cells (APCs). This induces T-cells to promote clonal expansion, cytokine secretion and effector function. In the absence of co-stimulation, T-cells can become refractory to antigen stimulation, which results in a tolerogenic response to either foreign or endogenous antigens.

In the two-signal model, T-cells receive both positive co-stimulatory and negative co-inhibitory signals. The regulation of such positive and negative signals is critical to maximize the host's protective immune responses, while maintaining immune tolerance and preventing autoimmunity. Negative signals seem necessary for induction of T-cell tolerance, while positive signals promote T-cell activation. Both co-stimulatory and co-inhibitory signals are provided to antigen-exposed T cells, and the interplay between co-stimulatory and co-inhibitory signals is essential to controlling the magnitude of an immune response. Further, the signals provided to the T cells change as an infection or immune provocation is cleared, worsens, or persists, and these changes powerfully affect the responding T cells and re-shape the immune response.

The mechanism of co-stimulation is of therapeutic interest because the manipulation of co-stimulatory signals has shown to provide a means to either enhance or terminate cell-based immune response. Recently, it has been discovered that T cell dysfunction or anergy can occur concurrently with an induced and sustained expression of immune checkpoint regulators, such as programmed death 1 polypeptide (PD-1) and its ligands, PD-L1 and PD-L2. PD-L1 is over-expressed in many cancers and is often associated with poor prognosis (Thompson R H et al., *Cancer Res* 2006, 66(7): 3381). Further, the majority of tumor infiltrating T lymphocytes predominantly express PD-1, in contrast to T lymphocytes in normal tissues and peripheral blood T lymphocytes indicating that up-regulation of PD-1 on tumor-reactive T

cells can contribute to impaired antitumor immune responses (Blood 2009 114(8):1537). This may be due to exploitation of PD-L1 signaling mediated by PD-L1 expressing tumor cells interacting with PD-1 expressing T cells to result in attenuation of T cell activation and evasion of immune surveillance. Inhibition of the PD-L1/PD-1 interaction provides a means to enhance T cell immunity, including CD8+ T cell-mediated killing of cancer cells and tumors. Similar enhancements to T cell immunity have been observed by inhibiting the binding of PD-L1 to the binding partner B7-1. Consequently, therapeutic targeting of PD-1 and other immune checkpoint regulators are an area of intense interest.

Combining inhibition of TIGIT, PD-1, PD-L1 and/or LAG-3 signaling with other signaling pathways deregulated in tumor cells can provide a means for enhance treatment efficacy. In recent years, a number of immune checkpoint regulators in the form of receptors and their ligands have been identified. One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes CTLA-4 and its ligands, B7-1 and B7-2; PD-1 and its ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC); B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Additional immune checkpoint antagonists include, but are not limited to TIM-3 and its ligand, Galectin-9; LAG-3 and its ligands, including liver sinusoidal endothelial cell lectin (LSECtin) and Galectin-3; CD122 and its CD122R ligand; CD70, B7H3, B and T lymphocyte attenuator (BTLA), and VISTA (Le Mercier et al. (2015) *Front. Immunol.*, (6), Article 418). In addition, a number of checkpoint regulator antagonists have been identified and tested in various clinical and pre-clinical models and/or approved by the FDA (Kyi et al., *FEBS Letters*, 588:368-376 (2014)). The concept of inhibitory receptor blockade, also known as immune checkpoint blockade, has been validated by virtue of e.g., the FDA approval of the PD-1 inhibitors, nivolumab and pembrolizumab, as well as the anti-CTLA-4 antibody, ipilimumab for metastatic melanoma.

An immune checkpoint antagonist modulates or interferes with the activity of the immune checkpoint regulator so that, as a result of the binding to the checkpoint regulator or its ligand, signaling through the checkpoint regulator receptor is blocked or inhibited. By inhibiting this signaling, immune-suppression can be reversed so that T cell immunity against cancer cells can be re-established or enhanced. In contrast, an immune checkpoint agonist (of e.g., a costimulatory molecule) stimulates the activity of an immune checkpoint regulator so that, as a result of the binding to the checkpoint regulator or its ligand, signaling through the checkpoint regulator receptor is stimulated. By stimulating this signaling, T cell immunity against cancer cells can be re-established or enhanced.

Accordingly, in one embodiment, a method for stimulating an immune response in a subject comprises administering to the subject an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, antibody fragment(s) thereof (e.g., anti-TIGIT HCVR and/LCVRs) or bispecific antitumor antagonist described herein in combination with another immune checkpoint regulator described herein above, such that an immune response is stimulated in the subject, for example to inhibit tumor growth or to stimulate an anti-viral response.

In one embodiment, an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, antibody fragment(s) thereof, or bispecific antitumor antagonist, according to the present application is administered in

combination with another immune checkpoint regulator, either as separate antibodies or in multi-specific antibody comprising binding specificities to multiple products. Generally, an anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody, or bispecific antitumor antagonist, described herein can be combined to stimulate an immune response with (i) an antagonist of the IgSF family protein, B7 family or TNF family that inhibit T cell activation, or antagonist of a cytokine that inhibits T cell activation (e.g., IL-6, IL-10, TGF- β , VEGF, or other immunosuppressive cytokines) and/or (ii) an agonist of a stimulatory receptors of the IgSF family, B7 family or TNF family or of cytokines to stimulate T cell activation, for stimulating an immune response.

In one embodiment, the subject is administered an anti-TIGIT antibody or HCVR and/or LCVR fragments thereof in combination with an anti-PD-1 antibody or PD-1 antagonist. In another embodiment, the subject is administered is administered an anti-TIGIT antibody or HCVR and/or LCVR fragments thereof in combination with an anti-PD-L1 antibody or PD-L1 antagonist. In another embodiment, the subject is administered an anti-TIGIT antibody or HCVR and/or LCVR fragments thereof in combination with an anti-CTLA-4 antibody or CTLA-4 antagonist.

In certain embodiments, only subjects with a cancer exhibiting high expression of a ligand for an immune checkpoint regulator are selected for combination treatment with the anti-TIGIT, anti-PD-1, anti-PD-L1 and/or anti-LAG-3 antibody, fragment thereof, or any of the bispecific antagonists of the present application. By way of example, in one embodiment, a subject with a cancer exhibiting high expression of PVR (CD155) and/or Nectin-2 (CD112) and/or low expression PD-L1 may be selected for monotherapy with anti-TIGIT antibodies, fragments thereof, or TIGIT antagonists of the present application, or combination therapy with a PD-1 antagonist or other immune checkpoint regulator.

The anti-TIGIT antibody, anti-PD-1 antibody, anti-PD-L1 antibody may be administered separately from the second antibody, antibody fragment or antagonist, or a multispecific antibody or antagonist may be administered comprising at least one binding specificity for TIGIT and a second binding specificity for the other targeted product. Further, the anti-TIGIT, anti-PD-1 antibody, anti-PD-L1 antibody, anti-LAG-3 antibody or bispecific antagonist in accordance with the present application may be co-administered with one or more additional agents, e.g., antibodies, antagonists, or drugs in amount(s) effective in stimulating an immune response and/or apoptosis so as to further enhance, stimulate or upregulate an immune response and/or apoptosis in a subject.

In some embodiments, the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody or fragment(s) thereof is administered subsequent to treatment with a different antitumor antagonist. For example, in one embodiment, anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibodies may be administered only after treatment with a PD-1/PD-L1 antagonist has failed, has led to incomplete therapeutic response, or there has been recurrence of the tumor or relapse (or "PD-1 failure"). In some embodiments, cancers exhibiting such failures may be screened for expression of e.g., PVR and/or Nectin-2 and only those having high level expression are treated with an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody, fragment or antagonist of the present application.

In one embodiment, the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody or fragment(s) thereof are administered in combination with a PD-1, PD-L1, PD-L2, TIGIT, or LAG-3 antagonist.

Other anti-PD-1 antibodies include, but are not limited to, nivolumab (BMS-936558, MDX-1106, OPDIVO™), a humanized immunoglobulin G4 (IgG4) mAb (Bristol-Myers Squibb); pembrolizumab (MK-3475, lambrolizumab, KEYTRUDA™) (Merck); pidilizumab (CT-011) (Medivation); and AMP-224 (Merck). Anti-PD-1 antibodies are commercially available, for example from ABCAM (AB137132), BIOLEGEND™ (EH12.2H7, RMP1-14) and AFFYMETRIX EBIOSCIENCE (J105, J116, MIH4).

Other anti-PD-L1 antibodies include atezolizumab (MPDL3280A, RG7446), a fully human IgG4 mAb Genentech/Roche); BMS-936559 (MDX-1105), a fully humanized IgG4 mAb (Bristol-Myers Squibb); MEDI4736, a humanized IgG antibody (Medimmune/AstraZeneca); and MSB0010718C, a fully human IgG4 monoclonal antibody (Merck, EMD Serono).

Exemplary anti-CTLA-4 antibodies for use in accordance with the present methods include ipilimumab, trevilizumab and tremelimumab.

In certain embodiments, the antitumor antagonist is a dominant negative protein of the immune checkpoint regulator. In particular embodiments, the dominant negative protein comprises an extracellular domain derived from a member selected from the group consisting of PD-L1, PD-L2, PD-1, B7-1, B7-2, B7H3, CTLA-4, LAG-3, TIM-3, TIGIT, BTLA, VISTA, CD70, and combinations thereof. In certain particular embodiments, these extracellular domains are fused to an immunoglobulin constant region or Fc receptor in the presently described antibodies. Such mutants can bind to the endogenous receptor so as to form a complex that is deficient in signaling. In certain embodiments, the extracellular domain is fused to an immunoglobulin constant region or Fc fragment or to a monomer in the oligomeric protein complex.

In certain embodiments, a dominant negative PD-L1 antagonist comprises an extracellular domain of PD-1. An exemplary dominant negative protein is AMP-224 (co-developed by Glaxo Smith Kline and Amplimmune), a recombinant fusion protein comprising the extracellular domain of PD-L2 and the Fc region of human IgG. In another embodiment, a dominant-negative PD-L1 antagonist includes one or more mutation(s) in PD-1 preventing its ability to bind PD-L1.

Exemplary immune checkpoint regulator agonists include, but are not limited to members of the tumor necrosis factor (TNF) receptor superfamily, such as CD27, CD40, OX40, GITR and 4-1BB (CD137) and their ligands, or members of the B7-CD28 superfamily, including CD28 and ICOS (CD278). Additional checkpoint regulator agonists include CD2, CDS, ICAM-1, LFA-1 (CD11a/CD18), CD30, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, CD83 ligand. Immune checkpoint agonists can include antibodies or soluble fusion protein agonists comprising one or more costimulatory domains. Agonist antibodies include, but are not limited to anti-CD40 mAbs, such as CP-870,893, lucatumumab, and dacetuzumab; anti-CD137 mAbs, such as BMS-663513 urelumab, and PF-05082566; anti-OX40 mAbs; anti-GITR mAbs, such as TRX518; anti-CD27 mAbs, such as CDX-1127; and anti-ICOS mAbs.

Exemplary GITR agonists include, e.g., GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies) such as, e.g., a GITR fusion protein described in

U.S. Pat. Nos. 6,111,090 and 8,586,023; European Patent No.: 090505B1, U.S. Pat. No. PCT Publication Nos.: WO 2010/003118 and 2011/090754. Anti-GITR antibodies are described in, e.g., in U.S. Pat. Nos. 7,025,962, 7,618,632, 7,812,135, 8,388,967, and 8,591,886; European Patent Nos.: 1947183B1 and 1866339; PCT Publication Nos.: WO 2011/028683, WO 2013/039954, WO2005/007190, WO 2007/133822, WO2005/055808, WO 99/40196, WO 2001/03720, WO99/20758, WO2006/083289, WO 2005/115451, WO 2011/051726. An exemplary anti-GITR antibody is TRX518.

Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which include CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137/4-1BB, TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT β R, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α /TNF γ , TNFR2, TNF α , LT β R, Lymphotoxin α 1(32, FAS, FASL, RELT, DR6, TROY, NGFR (see, e.g., Tansey, M. G. et al. (2009) Drug Discovery Today, 14(23-24):1082-1088).

Immune checkpoint agonists or costimulatory molecules include cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response, and include, but are not limited to MEW class I molecules, MEW class II molecules, TNF receptor proteins, immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRP1), NKp44, NKp30, NKp46, CD19, CD4, CD8 α , CD8 β , IL2R β , IL2R γ , IL7R α , ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

In one aspect, T cell responses can be stimulated by a combination of the anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 mAbs of the present invention and one or more of (i) an antagonist of a protein that inhibits T cell activation (e.g., immune checkpoint inhibitors), such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD-1H, LAIR1, TIM-1, CD96 and TIM-4, and (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, CD40, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

Exemplary agents that modulate one of the above proteins and may be combined with the anti-TIGIT antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, and/or anti-LAG-3 antibodies of the present application for treating cancer, include: YERVOYTM/ipilimumab or tremelimumab

(to CTLA-4), galiximab (to B7.1), OPDIVOTM/nivolumab/BMS-936558 (to PD-1), pidilizumab/CT-011 (to PD-1), KEYTRUDATM/pembrolizumab/MK-3475 (to PD-1), AMP224 (to B7-DC/PD-L2), BMS-936559 (to B7-H1), MPDL3280A (to B7-H1), MEDI-570 (to ICOS), AMG557 (to B7H2), MGA271 (to B7H3), IMP321 (to LAG-3), urelumab/BMS-663513 and PF-05082566 (to CD137/4-1BB), CDX-1127 (to CD27), MEDI-6383 and MEDI-6469 (to OX40), RG-7888 (to OX40L), Atacicept (to TACI), CP-870893 (to CD40), lucatumumab (to CD40), dacetuzumab (to CD40), and muromonab-CD3 (to CD3).

Other molecules that can be combined with the antitumor antagonists described herein for the treatment of cancer include antagonists of inhibitory receptors on NK cells or agonists of activating receptors on NK cells. For example, antagonist anti-TIGIT, anti-PD-1, and/or anti-PD-L1 antibodies can be combined with antagonists of KIR (e.g., lirilumab), CSF-1R antagonists, such as RG7155.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of immunosuppressive proteins expressed by the tumors. These include among others TGF- β , IL-10, and Fas ligand. Antibodies to each of these entities can be used in combination with the antitumor antagonists described herein to counteract the effects of the immunosuppressive agent and favor tumor immune responses by the host.

Other antibodies that activate host immune responsiveness can be used in combination with the antitumor antagonists described herein. These include molecules on the surface of dendritic cells that activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity and can be used in conjunction with the antitumor antagonists described herein. Activating antibodies to T cell costimulatory molecules such as OX-40, CD137/4-1BB, and ICOS may also provide for increased levels of T cell activation.

In certain embodiments, the antitumor antagonists described herein can be co-administered with one or other more therapeutic agents, e.g., anti-cancer agents, radiotoxic agents or an immunosuppressive agent. Such co-administration can solve problems due to development of resistance to drugs, changes in the antigenicity of the tumor cells that would render them unreactive to the antibody, and toxicities (by administering lower doses of one or more agents).

The antitumor antagonists described herein can be linked to the agent (as an immuno-complex) or can be administered separate from the agent. In the latter case (separate administration), the antibody can be administered before, after or concurrently with the agent or can be co-administered with other known therapies, e.g., an anti-cancer therapy, e.g., radiation. The antitumor antagonists described herein may be co-administered with one or more anti-cancer agents so as to provide two anti-cancer agents operating synergistically via different mechanisms to yield a cytotoxic effect in human cancer cells.

The antitumor antagonists described herein may be combined with an anti-cancer agent, such an alkylating agent; an anthracycline antibiotic; an anti-metabolite; a detoxifying agent; an interferon; a polyclonal or monoclonal antibody; an EGFR inhibitor; a HER2 inhibitor; a histone deacetylase inhibitor; a hormone; a mitotic inhibitor; a phosphatidylinositol-3-kinase (PI3K) inhibitor; an Akt inhibitor; a mammalian target of rapamycin (mTOR) inhibitor; a proteasomal inhibitor; a poly(ADP-ribose) polymerase (PARP) inhibitor; a Ras/MAPK pathway inhibitor; a centrosome declustering agent; a multi-kinase inhibitor; a serine/threo-

nine kinase inhibitor; a tyrosine kinase inhibitor; a VEGF/VEGFR inhibitor; a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, an inhibitor of a molecular target or enzyme (e.g., a kinase or a protein methyltransferase), a cytidine analogue or combination thereof.

Exemplary alkylating agents include, but are not limited to, cyclophosphamide (Cytoxan; Neosar); chlorambucil (Leukeran); melphalan (Alkeran); carmustine (BiCNU); busulfan (Busulfex); lomustine (CeeNU); dacarbazine (DTIC-Dome); oxaliplatin (Eloxatin); carmustine (Gliadel); ifosfamide (Ifex); mechlorethamine (Mustargen); busulfan (Myleran); carboplatin (Paraplatin); cisplatin (CDDP; Platinol); temozolomide (Temodar); thiotepe (Thioplex); bendamustine (Treanda); or streptozocin (Zanosar).

Exemplary anthracycline antibiotics include, but are not limited to, doxorubicin (Adriamycin); doxorubicin liposomal (Doxil); mitoxantrone (Novantrone); bleomycin (Blenoxane); daunorubicin (Cerubidine); daunorubicin liposomal (DaunoXome); dactinomycin (Cosmegen); epirubicin (Ellence); idarubicin (Idamycin); plicamycin (Mithracin); mitomycin (Mutamycin); pentostatin (Nipent); or valrubicin (Valstar).

Exemplary anti-metabolites include, but are not limited to, fluorouracil (Adrucil); capecitabine (Xeloda); hydroxyurea (Hydrea); mercaptopurine (Purinethol); pemetrexed (Alimta); fludarabine (Fludara); nelarabine (Arranon); cladribine (Cladribine Novaplus); clofarabine (Clozar); cytarabine (Cytosar-U); decitabine (Dacogen); cytarabine liposomal (DepoCyt); hydroxyurea (Droxia); pralatrexate (Folotylin); floxuridine (FUDR); gemcitabine (Gemzar); cladribine (Leustatin); fludarabine (Oforta); methotrexate (MTX; Rheumatex); methotrexate (Trexall); thioguanine (Tabloid); TS-1 or cytarabine (Tarabine PFS).

Exemplary detoxifying agents include, but are not limited to, amifostine (Ethyol) or mesna (Mesnex).

Exemplary interferons include, but are not limited to, interferon alfa-2b (Intron A) or interferon alfa-2a (Roferon-A).

Exemplary polyclonal or monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin); ofatumumab (Arzerra); bevacizumab (Avastin); rituximab (Rituxan); cetuximab (Erbix); panitumumab (Vectibix); tositumomab/iodine131 tositumomab (Bexxar); alemtuzumab (Campath); ibritumomab (Zevalin; In-111; Y-90 Zevalin); gemtuzumab (Mylotarg); eculizumab (Soliris) ordenosumab.

Exemplary EGFR inhibitors include, but are not limited to, gefitinib (Iressa); lapatinib (Tykerb); cetuximab (Erbix); erlotinib (Tarceva); panitumumab (Vectibix); PKI-166; canertinib (CI-1033); matuzumab (Emd7200) or EKB-569.

Exemplary HER2 inhibitors include, but are not limited to, trastuzumab (Herceptin); lapatinib (Tykerb) or AC-480.

Exemplary histone deacetylase inhibitors include, but are not limited to, vorinostat (Zolinza), valproic acid, romidepsin, entinostat abexinostat, givinostat, and mocetinostat.

Exemplary hormones include, but are not limited to, tamoxifen (Soltamox; Nolvadex); raloxifene (Evista); megestrol (Megace); leuprolide (Lupron; Lupron Depot; Eligard; Viadur); fulvestrant (Faslodex); letrozole (Femara); triptorelin (Trelstar LA; Trelstar Depot); exemestane (Aromasin); goserelin (Zoladex); bicalutamide (Casodex); anastrozole (Arimidex); fluoxymesterone (Androxy; Halotestin); medroxyprogesterone (Provera; Depo-Provera); estramustine (Emcyt); flutamide (Eulexin); toremifene (Fareston); degarelix (Firmagon); nilutamide (Nilandron); abarelix (Plenaxis); or testolactone (Teslac).

Exemplary mitotic inhibitors include, but are not limited to, paclitaxel (Taxol; Onxol; Abraxane); docetaxel (Taxotere); vincristine (Oncovin; Vincasar PFS); vinblastine (Velban); etoposide (Toposar; Etopophos; VePesid); teniposide (Vumon); ixabepilone (Ixempra); nocodazole; epothilone; vinorelbine (Navelbine); camptothecin (CPT); irinotecan (Camptosar); topotecan (Hycamtin); amsacrine or lamellarin D (LAM-D).

Exemplary phosphatidylinositol-3 kinase (PI3K) inhibitors include wortmannin an irreversible inhibitor of PI3K, demethoxyviridin a derivative of wortmannin, LY294002, a reversible inhibitor of PI3K; BKM120 (Buparlisib); Idelalisib (a PI3K Delta inhibitor); duvelisib (IPI-145, an inhibitor of PI3K delta and gamma); alpelisib (BYL719), an alpha-specific PI3K inhibitor; TGR 1202 (previously known as RP5264), an oral PI3K delta inhibitor; and copanlisib (BAY 80-6946), an inhibitor PI3K α,δ isoforms predominantly.

Exemplary Akt inhibitors include, but are not limited to, miltefosine, AZD5363, GDC-0068, MK2206, Perifosine, RX-0201, PBI-05204, GSK2141795, and SR13668.

Exemplary MTOR inhibitors include, but are not limited to, everolimus (Afinitor) or temsirolimus (Torisel); rapamune, ridaforolimus; deforolimus (AP23573), AZD8055 (AstraZeneca), OSI-027 (OSI), INK-128, BEZ235, PI-103, Torin1, PP242, PP30, Ku-0063794, WAY-600, WYE-687, WYE-354, and CC-223.

Exemplary proteasomal inhibitors include, but are not limited to, bortezomib (PS-341), ixazomib (MLN 2238), MLN 9708, delanzomib (CEP-18770), carfilzomib (PR-171), YU101, oprozomib (ONX-0912), marizomib (NPI-0052), and disufiram.

Exemplary PARP inhibitors include, but are not limited to, olaparib, iniparib, velaparib, BMN-673, BSI-201, AG014699, ABT-888, GPI21016, MK4827, INO-1001, CEP-9722, PJ-34, Tiq-A, Phen, PF-01367338 and combinations thereof.

Exemplary Ras/MAPK pathway inhibitors include, but are not limited to, trametinib, selumetinib, cobimetinib, CI-1040, PD0325901, AS703026, R04987655, RO5068760, AZD6244, GSK1120212, TAK-733, U0126, MEK162, and GDC-0973.

Exemplary centrosome declustering agents include, but are not limited to, griseofulvin; noscapine, noscapine derivatives, such as brominated noscapine (e.g., 9-bromonoscapine), reduced bromonoscapine (RBN), N-(3-bromobenzyl) noscapine, aminonoscapine and water-soluble derivatives thereof; CW069; the phenanthridene-derived poly(ADP-ribose) polymerase inhibitor, PJ-34; N2-(3-pyridylmethyl)-5-nitro-2-furamide, N2-(2-thienylmethyl)-5-nitro-2-furamide, and N2-benzyl-5-nitro-2-furamide.

Exemplary multi-kinase inhibitors include, but are not limited to, regorafenib; sorafenib (Nexavar); sunitinib (Sutent); BIBW 2992; E7080; ZD6474; PKC-412; motesanib; or AP24534.

Exemplary serine/threonine kinase inhibitors include, but are not limited to, ruboxistaurin; eril/easudil hydrochloride; flavopiridol; seliciclib (CYC202; Roscovitine); SNS-032 (BMS-387032); Pkc412; bryostatin; KAI-9803; SF1126; VX-680; Azd1152; Arry-142886 (AZD-6244); SC10-469; GW681323; CC-401; CEP-1347 or PD 332991.

Exemplary tyrosine kinase inhibitors include, but are not limited to, erlotinib (Tarceva); gefitinib (Iressa); imatinib (Gleevec); sorafenib (Nexavar); sunitinib (Sutent); trastuzumab (Herceptin); bevacizumab (Avastin); rituximab (Rituxan); lapatinib (Tykerb); cetuximab (Erbix); panitumumab (Vectibix); everolimus (Afinitor); alemtuzumab (Campath); gemtuzumab (Mylotarg); temsirolimus (Tori-

sel); pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna); vatalanib (Ptk787; ZK222584); CEP-701; SU5614; MLN518; XL999; VX-322; Azd0530; BMS-354825; SKI-606 CP-690; AG-490; WHI-P154; WHI-P131; AC-220; or AMG888.

Exemplary VEGF/VEGFR inhibitors include, but are not limited to, bevacizumab (Avastin); sorafenib (Nexavar); sunitinib (Sutent); ranibizumab; pegaptanib; or vandetinib.

Exemplary microtubule targeting drugs include, but are not limited to, paclitaxel, docetaxel, vincristin, vinblastin, nocodazole, epothilones and navelbine.

Exemplary topoisomerase poison drugs include, but are not limited to, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin and idarubicin.

Exemplary taxanes or taxane derivatives include, but are not limited to, paclitaxel and docetaxol.

Exemplary general chemotherapeutic, anti-neoplastic, anti-proliferative agents include, but are not limited to, altretamine (Hexalen); isotretinoin (Accutane; Amnesteem; Claravis; Sotret); tretinoin (Vesanoid); azacitidine (Vidaza); bortezomib (Velcade) asparaginase (Elspar); levamisole (Ergamisol); mitotane (Lysodren); procarbazine (Matulane); pegaspargase (Oncaspar); denileukin diftitox (Ontak); porfimer (Photofrin); aldesleukin (Proleukin); lenalidomide (Revlimid); bexarotene (Targretin); thalidomide (Thalomid); temsirolimus (Torisel); arsenic trioxide (Trisenox); verteporfin (Visudyne); mimosine (Leucenol); (1M tegafur-0.4 M 5-chloro-2,4-dihydroxypyrimidine-1 M potassium oxonate) or lovastatin.

In certain embodiments, TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition is combined with standard cancer treatments (e.g., surgery, radiation, and chemotherapy). TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition can be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of chemotherapeutic reagent administered. An example of such a combination is an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody in combination with decarbazine for the treatment of melanoma. Another example of such a combination is an anti-TIGIT, anti-PD-1, anti-PD-L1 or anti-LAG-3 antibody in combination with interleukin-2 (IL-2) for the treatment of melanoma. It is believed that the combined use of TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition and chemotherapy can enhance apoptosis and increase tumor antigen presentation for cytotoxic immunity. Other synergistic combination therapies include TIGIT, PD-1, PD-L1 and/or LAG-3 inhibition through cell death when used in combination with radiation, surgery or hormone deprivation. Each of these protocols creates a source of tumor antigen in the host.

In certain embodiments, the checkpoint regulator antagonists described herein can be used in multi-specific antagonists or in combination with bispecific antibodies targeting Fc α or Fc γ receptor-expressing effector cells to tumor cells (see, e.g., U.S. Pat. Nos. 5,922,845 and 5,837,243). Bispecific antibodies can be used to target two separate antigens. For example anti-Fc receptor/anti-tumor antigen (e.g., Her-2/neu) bispecific antibodies have been used to target macrophages to cancer cells or tumors. This targeting may more effectively activate tumor specific responses. The T cell arm of these responses would be augmented by the inhibition of TIGIT, PD-1, PD-L1 and/or LAG-3. Alternatively, antigen may be delivered directly to DCs by the use of bispecific antibodies that bind to tumor antigen and a dendritic cell specific cell surface marker.

IV. Nucleic Acids and Host Cells for Expressing Checkpoint Regulator

In another aspect, the present application provides nucleic acids encoding the antitumor antagonists of the present application, including the heavy and light chains, as well as expression vectors comprising such nucleic acids. In particular, the nucleic acids encode one or more HCDRs, LCDRs, HCVRs and/or LCVRs corresponding to any of the antibodies, antagonists or fragments described herein.

Thus, in one aspect, the present application provides one or more nucleic acids encoding any of the antitumor antagonists, antibodies or antigen-binding portions thereof as described herein.

In another aspect, the present application provides one or more expression vectors comprising the one or more nucleic acids encoding any of the antitumor antagonists, antibodies or antigen-binding portions thereof as described herein.

In another aspect, the present application provides a host cell transformed with the one or more expression vectors comprising the one or more nucleic acids encoding any of the antitumor antagonists, antibodies or antigen-binding portions thereof as described herein.

DNA(s) encoding antigen binding sites can be isolated and sequenced from a monoclonal antibody produced in hybridoma cells using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Alternatively, amino acid sequences from immunoglobulins of interest may be determined by direct protein sequencing, and suitable encoding nucleotide sequences can be designed according to a universal codon table. In other cases, nucleotide and amino acid sequences of antigen binding sites or other immunoglobulin sequences, including constant regions, hinge regions and the like may be obtained from published sources well known in the art.

Expression vectors encoding a particular monospecific or bispecific antitumor antagonist may be used to synthesize the antitumor antagonists of the present disclosure in cultured cells in vitro or they may be directly administered to a patient to express the antitumor antagonist in vivo or ex vivo. As used herein, an "expression vector" refers to a viral or non-viral vector comprising a polynucleotide encoding one or more polypeptide chains corresponding to the monospecific or bispecific antitumor antagonists of the present disclosure in a form suitable for expression from the polynucleotide(s) in a host cell for antibody preparation purposes or for direct administration as a therapeutic agent.

A nucleic acid sequence is "operably linked" to another nucleic acid sequence when the former is placed into a functional relationship with the latter. For example, a DNA for a presequence or signal peptide is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous and, in the case of a signal peptide, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers may be used in accordance with conventional practice.

Nucleic acid sequences for expressing the antitumor antagonists typically include an amino terminal signal peptide sequence, which is removed from the mature protein. Since the signal peptide sequences can affect the levels of expression, the polynucleotides may encode any one of a variety of different N-terminal signal peptide sequences. It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like.

The above described "regulatory sequences" refer to DNA sequences necessary for the expression of an operably linked coding sequence in one or more host organisms. The term "regulatory sequences" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells or those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). Expression vectors generally contain sequences for transcriptional termination, and may additionally contain one or more elements positively affecting mRNA stability.

The expression vector contains one or more transcriptional regulatory elements, including promoters and/or enhancers, for directing the expression of antitumor antagonists. A promoter comprises a DNA sequence that functions to initiate transcription from a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic interaction of RNA polymerase and transcription factors, and may operate in conjunction with other upstream elements and response elements.

As used herein, the term "promoter" is to be taken in its broadest context and includes transcriptional regulatory elements (TREs) from genomic genes or chimeric TREs therefrom, including the TATA box or initiator element for accurate transcription initiation, with or without additional TREs (i.e., upstream activating sequences, transcription factor binding sites, enhancers, and silencers) which regulate activation or repression of genes operably linked thereto in response to developmental and/or external stimuli, and trans-acting regulatory proteins or nucleic acids. A promoter may contain a genomic fragment or it may contain a chimera of one or more TREs combined together.

Preferred promoters are those capable of directing high-level expression in a target cell of interest. The promoters may include constitutive promoters (e.g., HCMV, SV40, elongation factor-1 α (EF-1 α)) or those exhibiting preferential expression in a particular cell type of interest. Enhancers generally refer to DNA sequences that function away from the transcription start site and can be either 5' or 3' to the transcription unit. Furthermore, enhancers can be within an intron as well as within the coding sequence. They are usually between 10 and 300 bp in length, and they function in cis. Enhancers function to increase and/or regulate transcription from nearby promoters. Preferred enhancers are those directing high-level expression in the antibody producing cell. Cell or tissue-specific transcriptional regulatory elements (TREs) can be incorporated into expression vectors to restrict expression to desired cell types. Pol III promoters (H1 or U6) are particularly useful for expressing shRNAs from which siRNAs are expressed. An expression vector may be designed to facilitate expression of the antitumor antagonist in one or more cell types.

In certain embodiments, one or more expression vectors may be engineered to express both the antitumor antagonist

and one or more siRNA targeting the Tie2 pathway, the VEGF pathway or an immune checkpoint regulator.

An siRNA is a double-stranded RNA that can be engineered to induce sequence-specific post-transcriptional gene silencing of mRNAs. Synthetically produced siRNAs structurally mimic the types of siRNAs normally processed in cells by the enzyme Dicer. When expressed from an expression vector, the expression vector is engineered to transcribe a short double-stranded hairpin-like RNA (shRNA) that is processed into a targeted siRNA inside the cell. Synthetic siRNAs and shRNAs may be designed using well known algorithms and synthesized using a conventional DNA/RNA synthesizer.

To co-express the individual chains of the antitumor antagonist, a suitable splice donor and splice acceptor sequences may be incorporated for expressing both products. Alternatively, an internal ribosome binding sequence (IRES) or a 2A peptide sequence, may be employed for expressing multiple products from one promoter. An IRES provides a structure to which the ribosome can bind that does not need to be at the 5' end of the mRNA. It can therefore direct a ribosome to initiate translation at a second initiation codon within a mRNA, allowing more than one polypeptide to be produced from a single mRNA. A 2A peptide contains short sequences mediating co-translational self-cleavage of the peptides upstream and downstream from the 2A site, allowing production of two different proteins from a single transcript in equimolar amounts. CHYSEL is a non-limiting example of a 2A peptide, which causes a translating eukaryotic ribosome to release the growing polypeptide chain that it is synthesizing without dissociating from the mRNA. The ribosome continues translating, thereby producing a second polypeptide.

An expression vector may comprise a viral vector or a non-viral vector. A viral vectors may be derived from an adeno-associated virus (AAV), adenovirus, herpesvirus, vaccinia virus, poliovirus, poxvirus, a retrovirus (including a lentivirus, such as HIV-1 and HIV-2), Sindbis and other RNA viruses, alphavirus, astrovirus, coronavirus, orthomyxovirus, papovavirus, paramyxovirus, parvovirus, picornavirus, togaviruses and the like. A non-viral vector is simply a "naked" expression vector that is not packaged with virally derived components (e.g., capsids and/or envelopes).

In certain cases, these vectors may be engineered to target certain diseases or cell populations by using the targeting characteristics inherent to the virus vector or engineered into the virus vector. Specific cells may be "targeted" for delivery of polynucleotides, as well as expression. Thus, the term "targeting", in this case, may be based on the use of endogenous or heterologous binding agents in the form of capsids, envelope proteins, antibodies for delivery to specific cells, the use of tissue-specific regulatory elements for restricting expression to specific subset(s) of cells, or both.

In some embodiments, expression of the antibody chains is under the control of the regulatory element such as a tissue specific or ubiquitous promoter. In some embodiments, a ubiquitous promoter such as a CMV promoter, CMV-chicken beta-actin hybrid (CAG) promoter, a tissue specific or tumor-specific promoter to control the expression of a particular antibody heavy or light chain or single-chain derivative therefrom.

Non-viral expression vectors can be utilized for non-viral gene transfer, either by direct injection of naked DNA or by encapsulating the antitumor antagonist-encoding polynucleotides in liposomes, microparticles, microcapsules, virus-like particles, or erythrocyte ghosts. Such compositions can be further linked by chemical conjugation to targeting

domains to facilitate targeted delivery and/or entry of nucleic acids into desired cells of interest. In addition, plasmid vectors may be incubated with synthetic gene transfer molecules such as polymeric DNA-binding cations like polylysine, protamine, and albumin, and linked to cell targeting ligands such as asialoorosomucoid, insulin, galactose, lactose or transferrin.

Alternatively, naked DNA may be employed. Uptake efficiency of naked DNA may be improved by compaction or by using biodegradable latex beads. Such delivery may be improved further by treating the beads to increase hydrophobicity and thereby facilitate disruption of the endosome and release of the DNA into the cytoplasm.

V. Methods for Producing Monospecific or Multispecific Antibodies

In another aspect, the present application provides host cells transformed with the anti-TIGIT, anti-PD-1, anti-PD-L1 and/or anti-LAG-3 HCVRs and/or LCVRs, encoding nucleic acids or expression vectors, or nucleic acids/expression vectors encoding the monospecific or bispecific antitumor antagonist of the present application. The host cells can be any bacterial or eukaryotic cell capable of expressing the anti-TIGIT, anti-PD-1, anti-PD-L1 and/or anti-LAG-3 HCVRs and/or LCVRs encoding nucleic acids or expression vectors or any of the other co-administered antibodies or antagonists described herein.

In another aspect, a method of producing an antitumor antagonist comprises culturing a host cell transformed with one or more anti-TIGIT, anti-PD-1, anti-PD-L1 and/or anti-LAG-3 HCVRs and/or LCVRs encoding nucleic acids or expression vectors under conditions that allows production of the antibody or fragment, and purifying the antibody from the cell.

In a further aspect, the present application provides a method for producing an antibody comprising culturing a cell transiently or stably expressing one or more constructs encoding one or more polypeptide chains in the antibody; and purifying the antibody from the cultured cells. Any cell capable of producing a functional antibody may be used. In preferred embodiments, the antibody-expressing cell is of eukaryotic or mammalian origin, preferably a human cell. Cells from various tissue cell types may be used to express the antibodies. In other embodiments, the cell is a yeast cell, an insect cell or a bacterial cell. Preferably, the antibody-producing cell is stably transformed with a vector expressing the antibody.

One or more expression vectors encoding the antibody heavy or light chains can be introduced into a cell by any conventional method, such as by naked DNA technique, cationic lipid-mediated transfection, polymer-mediated transfection, peptide-mediated transfection, virus-mediated infection, physical or chemical agents or treatments, electroporation, etc. In addition, cells may be transfected with one or more expression vectors for expressing the antibody along with a selectable marker facilitating selection of stably transformed clones expressing the antibody. The antibodies produced by such cells may be collected and/or purified according to techniques known in the art, such as by centrifugation, chromatography, etc.

Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR), thymidine kinase, neomycin, neomycin analog G418, hygromycin, and puromycin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective

pressure. There are two widely used distinct categories of selective regimes. The first category is based on a cell's metabolism and the use of a mutant cell line which lacks the ability to grow independent of a supplemented media. Two examples are CHO DHFR⁻ cells and mouse LTK⁻ cells. These cells lack the ability to grow without the addition of such nutrients as thymidine or hypoxanthine. Because these cells lack certain genes necessary for a complete nucleotide synthesis pathway, they cannot survive unless the missing nucleotides are provided in a supplemented media. An alternative to supplementing the media is to introduce an intact DHFR or TK gene into cells lacking the respective genes, thus altering their growth requirements. Individual cells which were not transformed with the DHFR or TK gene will not be capable of survival in non-supplemented media.

The second category is dominant selection which refers to a selection scheme used in any cell type and does not require the use of a mutant cell line. These schemes typically use a drug to arrest growth of a host cell. Those cells which have a novel gene would express a protein conveying drug resistance and would survive the selection. Examples of such dominant selection use the drugs neomycin, mycophenolic acid, or hygromycin. The three examples employ bacterial genes under eukaryotic control to convey resistance to the appropriate drug G418 or neomycin (geneticin), xgpt (mycophenolic acid) or hygromycin, respectively. Others include the neomycin analog G418 and puromycin.

Exemplary antibody-expressing cells include human Jurkat, human embryonic kidney (HEK) 293, Chinese hamster ovary (CHO) cells, mouse WEHI fibrosarcoma cells, as well as unicellular protozoan species, such as *Leishmania tarentolae*. In addition, stably transformed, antibody producing cell lines may be produced using primary cells immortalized with c-myc or other immortalizing agents.

In one embodiment, the cell line comprises a stably transformed *Leishmania* cell line, such as *Leishmania tarentolae*. *Leishmania* are known to provide a robust, fast-growing unicellular host for high level expression of eukaryotic proteins exhibiting mammalian-type glycosylation patterns. A commercially available *Leishmania* eukaryotic expression kit is available (Jena Bioscience GmbH, Jena, Germany).

In some embodiments, the cell line expresses at least 1 mg, at least 2 mg, at least 5 mg, at least 10 mg, at least 20 mg, at least 50 mg, at least 100 mg, at least 200 mg, at least 300 mg, at least 400 mg, or at least 500 mg of the antibody/liter of culture.

The antibodies in the present application may be isolated from antibody expressing cells following culture and maintenance in any appropriate culture medium, such as RPMI, DMEM, and AIM V®. The antibodies can be purified using conventional protein purification methodologies (e.g., affinity purification, chromatography, etc.), including the use of Protein-A or Protein-G immunoaffinity purification. In some embodiments, antibodies are engineered for secretion into culture supernatants for isolation therefrom.

VI. Pharmaceutical Compositions and Methods of Treatment

Another aspect of the present application relates to pharmaceutical compositions and methods for treating a cell proliferative disorder, such as cancer, chronic infections, or immunologically compromised disease states. In one embodiment, the pharmaceutical composition comprises one or more antitumor antagonists of the present application.

In some embodiments, the antitumor antagonist(s) comprise one or more checkpoint regulator antagonists, such as anti-T cell Ig and ITIM domain (TIGIT) inhibitors, PD-1 inhibitors, PD-L1 inhibitors and LAG-3 inhibitors. The antagonist(s) are formulated together with a pharmaceutically acceptable carrier. Pharmaceutical composition of the present application may include one or more different antibodies, one or more multispecific antibodies, one or more immunoconjugates, or a combination thereof as described herein.

As described above, methods for using the pharmaceutical compositions described herein comprise administering to a subject in need thereof an effective amount of the pharmaceutical composition according to the present disclosure.

Any suitable route or mode of administration can be employed for providing the patient with a therapeutically or prophylactically effective dose of the antibody or antagonist. Exemplary routes or modes of administration include parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous, intratumoral), oral, topical (nasal, transdermal, intradermal or intraocular), mucosal (e.g., nasal, sublingual, buccal, rectal, vaginal), inhalation, intralymphatic, intraspinal, intracranial, intraperitoneal, intratracheal, intravesical, intrathecal, enteral, intrapulmonary, intralymphatic, intracavitary, intraorbital, intracapsular and transurethral, as well as local delivery by catheter or stent.

A pharmaceutical composition comprising an antibody or antagonist in accordance with the present disclosure may be formulated in any pharmaceutically acceptable carrier(s) or excipient(s). As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Pharmaceutical compositions may comprise suitable solid or gel phase carriers or excipients. Exemplary carriers or excipients include but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Exemplary pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the therapeutic agents.

The antitumor antagonist can be incorporated into a pharmaceutical composition suitable for parenteral administration. Suitable buffers include but are not limited to, sodium succinate, sodium citrate, sodium phosphate or potassium phosphate. Sodium chloride can be used to modify the toxicity of the solution at a concentration of 0-300 mM (optimally 150 mM for a liquid dosage form). Cryoprotectants can be included for a lyophilized dosage form, principally 0-10% sucrose (optimally 0.5-1.0%). Other suitable cryoprotectants include trehalose and lactose. Bulking agents can be included for a lyophilized dosage form, principally 1-10% mannitol (optimally 2-4%). Stabilizers can be used in both liquid and lyophilized dosage forms, principally 1-50 mM L-Methionine (optimally 5-10 mM). Other suitable bulking agents include glycine, arginine, can be included as 0-0.05% polysorbate-80 (optimally 0.005-0.01%). Additional surfactants include but are not limited to polysorbate 20 and BRIJ surfactants.

Therapeutic antitumor antagonist preparations can be lyophilized and stored as sterile powders, preferably under vacuum, and then reconstituted in bacteriostatic water (containing, for example, benzyl alcohol preservative) or in sterile water prior to injection. Pharmaceutical composition may be formulated for parenteral administration by injection e.g., by bolus injection or continuous infusion.

The therapeutic agents in the pharmaceutical compositions may be formulated in a "therapeutically effective amount" or a "prophylactically effective amount". A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the recombinant vector may vary depending on the condition to be treated, the severity and course of the condition, the mode of administration, whether the antibody or agent is administered for preventive or therapeutic purposes, the bioavailability of the particular agent(s), the ability of the antitumor antagonist to elicit a desired response in the individual, previous therapy, the age, weight and sex of the patient, the patient's clinical history and response to the antibody, the type of the antitumor antagonist used, discretion of the attending physician, etc. A therapeutically effective amount is also one in which any toxic or detrimental effects of the recombinant vector is outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result.

Preferably, the polypeptide domains in the antitumor antagonist are derived from the same host in which they are to be administered in order to reduce inflammatory responses against the administered therapeutic agents.

The antitumor antagonist is suitably administered to the patient at one time or over a series of treatments and may be administered to the patient at any time from diagnosis onwards. The antitumor antagonist may be administered as the sole treatment or in conjunction with other drugs or therapies useful in treating the condition in question.

As a general proposition, a therapeutically effective amount or prophylactically effective amount of the antitumor antagonist will be administered in a range from about 1 ng/kg body weight/day to about 100 mg/kg body weight/day whether by one or more administrations. In a particular embodiment, each antitumor antagonist is administered in the range of from about 1 ng/kg body weight/day to about 10 mg/kg body weight/day, about 1 ng/kg body weight/day to about 1 mg/kg body weight/day, about 1 ng/kg body weight/day to about 100 µg/kg body weight/day, about 1 ng/kg body weight/day to about 10 µg/kg body weight/day, about 1 ng/kg body weight/day to about 1 µg/kg body weight/day, about 1 ng/kg body weight/day to about 100 ng/kg body weight/day, about 1 ng/kg body weight/day to about 10 ng/kg body weight/day, about 10 ng/kg body weight/day to about 100 mg/kg body weight/day, about 10 ng/kg body weight/day to about 10 mg/kg body weight/day, about 10 ng/kg body weight/day to about 1 mg/kg body weight/day, about 10 ng/kg body weight/day to about 100 µg/kg body weight/day, about 10 ng/kg body weight/day to about 10 µg/kg body weight/day, about 10 ng/kg body weight/day to about 1 µg/kg body weight/day, 10 ng/kg body weight/day to about 100 ng/kg body weight/day, about 100 ng/kg body weight/day to about 100 mg/kg body weight/day, about 100 ng/kg body weight/day to about 10 mg/kg body weight/day, about 100 ng/kg body weight/day to about 1 mg/kg body weight/day, about 100 ng/kg body weight/day to about 100 µg/kg body weight/day, about 100 ng/kg body weight/day to

55

about 10 µg/kg body weight/day, about 100 ng/kg body weight/day to about 1 µg/kg body weight/day, about 1 µg/kg body weight/day to about 100 mg/kg body weight/day, about 1 µg/kg body weight/day to about 10 mg/kg body weight/day, about 1 µg/kg body weight/day to about 1 mg/kg body weight/day, about 1 µg/kg body weight/day to about 100 µg/kg body weight/day, about 1 µg/kg body weight/day to about 10 µg/kg body weight/day, about 10 µg/kg body weight/day to about 100 mg/kg body weight/day, about 10 µg/kg body weight/day to about 10 mg/kg body weight/day, about 10 µg/kg body weight/day to about 1 mg/kg body weight/day, about 10 µg/kg body weight/day to about 100 µg/kg body weight/day, about 100 µg/kg body weight/day to about 100 mg/kg body weight/day, about 100 µg/kg body weight/day to about 10 mg/kg body weight/day, about 100 µg/kg body weight/day to about 1 mg/kg body weight/day, about 1 mg/kg body weight/day to about 100 mg/kg body weight/day, about 1 mg/kg body weight/day to about 10 mg/kg body weight/day, about 10 mg/kg body weight/day to about 100 mg/kg body weight/day.

In other embodiments, the antitumor antagonist is administered at a dose of 500 µg to 20 g every three days, or 25 mg/kg body weight every three days.

In other embodiments, each antitumor antagonist is administered in the range of about 10 ng to about 100 ng per individual administration, about 10 ng to about 1 µg per individual administration, about 10 ng to about 10 µg per individual administration, about 10 ng to about 100 µg per individual administration, about 10 ng to about 1 mg per individual administration, about 10 ng to about 10 mg per individual administration, about 10 ng to about 100 mg per individual administration, about 10 ng to about 1000 mg per injection, about 10 ng to about 10,000 mg per individual administration, about 100 ng to about 1 µg per individual administration, about 100 ng to about 10 µg per individual administration, about 100 ng to about 100 µg per individual administration, about 100 ng to about 1 mg per individual administration, about 100 ng to about 10 mg per individual administration, about 100 ng to about 100 mg per individual administration, about 100 ng to about 1000 mg per injection, about 100 ng to about 10,000 mg per individual administration, about 1 µg to about 10 µg per individual administration, about 1 µg to about 100 µg per individual administration, about 1 µg to about 1 mg per individual administration, about 1 µg to about 10 mg per individual administration, about 1 µg to about 100 mg per individual administration, about 1 µg to about 1000 mg per injection, about 1 µg to about 10,000 mg per individual administration, about 10 µg to about 100 µg per individual administration, about 10 µg to about 1 mg per individual administration, about 10 µg to about 10 mg per individual administration, about 10 µg to about 100 mg per individual administration, about 10 µg to about 1000 mg per injection, about 10 µg to about 10,000 mg per individual administration, about 100 µg to about 1 mg per individual administration, about 100 µg to about 10 mg per individual administration, about 100 µg to about 100 mg per individual administration, about 100 µg to about 1000 mg per injection, about 100 µg to about 10,000 mg per individual administration, about 1 mg to about 10 mg per individual administration, about 1 mg to about 100 mg per individual administration, about 1 mg to about 1000 mg per injection, about 1 mg to about 10,000 mg per individual administration, about 10 mg to about 100 mg per individual administration, about 10 mg to about 1000 mg per injection, about 10 mg to about 10,000 mg per individual administration, about 100 mg to about 1000 mg per injection, about 100 mg to about 10,000 mg per individual administration

56

and about 1000 mg to about 10,000 mg per individual administration. The antitumor antagonist may be administered daily, every 2, 3, 4, 5, 6 or 7 days, or every 1, 2, 3 or 4 weeks.

In other particular embodiments, the amount of the antitumor antagonist may be administered at a dose of about 0.0006 mg/day, 0.001 mg/day, 0.003 mg/day, 0.006 mg/day, 0.01 mg/day, 0.03 mg/day, 0.06 mg/day, 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, 1 mg/day, 3 mg/day, 6 mg/day, 10 mg/day, 30 mg/day, 60 mg/day, 100 mg/day, 300 mg/day, 600 mg/day, 1000 mg/day, 2000 mg/day, 5000 mg/day or 10,000 mg/day. As expected, the dosage will be dependent on the condition, size, age and condition of the patient.

In certain embodiments, the coding sequences for an antitumor antagonist are incorporated into a suitable expression vector (e.g., viral or non-viral vector) for expressing an effective amount of the antitumor antagonist in patient with a cell proliferative disorder. In certain embodiments comprising administration of e.g., one or more recombinant AAV (rAAV) viruses, the pharmaceutical composition may comprise the rAAVs in an amount comprising at least 10^{10} , at least 10^{11} , at least 10^{12} , at least 10^{13} , or at least 10^{14} genome copies (GC) or recombinant viral particles per kg, or any range thereof. In certain embodiments, the pharmaceutical composition comprises an effective amount of the recombinant virus, such as rAAV, in an amount comprising at least 10^{10} , at least 10^{11} , at least 10^{12} , at least 10^{13} , at least 10^{14} , at least 10^{15} genome copies or recombinant viral particles genome copies per subject, or any range thereof.

Dosages can be tested in several art-accepted animal models suitable for any particular cell proliferative disorder.

Delivery methodologies may also include the use of polycationic condensed DNA linked or unlinked to killed viruses, ligand linked DNA, liposomes, eukaryotic cell delivery vehicles cells, deposition of photopolymerized hydrogel materials, use of a handheld gene transfer particle gun, ionizing radiation, nucleic charge neutralization or fusion with cell membranes, particle mediated gene transfer and the like.

The present invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures and Tables are incorporated herein by reference.

EXAMPLES

Example 1: Generation of Monoclonal Antibodies

Monoclonal antibodies (mAbs) of the present application are generated and screened using techniques well known in the art, see, e.g., Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York. The antigen specific hybridoma mAbs are cloned, sequenced and engineered using techniques well known in the art, see e.g., Lo. B. K. C *Methods in Molecular Biology*TM. Volume 248 2004. Antibody Engineering.

FIG. 1 shows CDR sequences of anti-TIGIT mAbs. FIGS. 2A-2B show several embodiments of anti-TIGIT antibody variable domain sequences. FIG. 3 shows CDR sequences of anti-PD-1 mAbs. FIGS. 4A-4C show several embodiments of anti-PD-1 antibody variable domain sequences. FIG. 5 shows CDR sequences of anti-PD-L1 mAbs. FIGS. 6A-6C show several embodiments of anti-PD-L1 antibody variable domain sequences.

Example 2: Design of Bispecific Anti-PD-1
Antibodies with Anti-TIGIT scFv

FIGS. 7A-7C show three exemplary bispecific antitumor antagonists, Bi-TPM-93 (FIG. 7A), Bi-TPM-94A (FIG. 7B), and Bi-TPM-94B (FIG. 7C). These antagonists contain an anti-PD-1 (PD-01) antibody backbone (FIG. 7A) or an anti-PD-1 (PD-06/2P17) antibody backbone (FIGS. 7A, 7B) along with an anti-TIGIT scFv with heavy chain and light chain variable regions from the anti-TIGIT mAb T-10B21 separated by a 3xG4S linker (FIGS. 7A, 7B) or a 6xG4S linker (FIG. 7C).

FIG. 8 shows functional domain sequences present in the bispecific antibodies depicted in FIGS. 7A-7C.

FIGS. 9A-9B show exemplary heavy chain (HC) and light chain (LC) sequences corresponding to the bispecific antibodies depicted in FIGS. 7A-7C.

Example 3: Expression and Functional
Characterization of Bispecific Anti-Pd-1/Anti-Tigit
Antibodies

To evaluate the PD-1 blocking ability of Bi-TPM-93 and Bi-TPM-94A, a PD-1 IC₅₀ assay was conducted in which serial dilutions of the bispecific mAbs were incubated at 4° C. for 30 mins with human PD-1 transfected CHOK1 cells and 7 µg/ml FITC labeled human PD-L1-Fc protein, followed by washing and fixation of the cells prior to analysis with an iQue intellicyt system. The results of this assay in FIG. 10 show that Bi-TPM-94 containing VH and VL sequences from PD-06/2P17 blocks the interaction between PD-1 and its ligand, PD-L1 better (IC₅₀=0.15 nM) than Bi-TPM-93 containing VH and VL sequences from PD-01 (IC₅₀=0.83 nM).

FIG. 11 shows a non reducing PAGE analysis demonstrating robust transient expression of both Bi-TPM-94A and Bi-TPM-94B in human embryonic kidney (HEK) 293 cells.

To evaluate the degree of homogeneity of the antagonist species corresponding to Bi-TPM93, Bi-TPM-94A, and Bi-TPM-94B, the samples were purified and subjected to a size-exclusion ultra-high performance liquid chromatography (SE-UHPLC) analysis. Purification of the samples was carried out as follows. First, harvested cell culture fluids (HCCFs) were subjected to 0.2 µm filtration following by affinity purification using Hitrap Protein AHP chromatography (GE Healthcare) at 1 mL/min. Following affinity purification, the material was subjected to cation exchange (CEX) chromatography using Sepax Proteomix® SCX-NP5 columns with gradient elution at 0.8 mL/min. The amounts of aggregate (high molecular weight, HMW), dimer, and low molecular weight (LMW) fragments were determined by SE-UPLC using Tosoh TSKgel UP-G3000SWXL columns.

The results of this analysis (FIG. 12) unexpectedly revealed a level of species heterogeneity in Bi-TPM 93 and Bi-TPM-94A that was eliminated by linker modification in Bi-TPM-94B, i.e., increasing the length of linker from 3xG4S to 6xG4S.

To evaluate the binding affinities and kinetics of binding to His tagged human PD-1 by Bi-TPM-94A, Bi-TPM-94B, and a parental anti-PD-1 benchmark (BM) mAb, bio-layer interferometry was carried out using the Octet RED96 system (ForteBio). Briefly, 20 nM of the bispecific antagonist were loaded onto anti-human IgG capture biosensors. Association of analyte (His tagged human PD-1 protein or His tagged human TIGIT protein) was observed by placing the biosensors in wells containing serial dilution of His

tagged PD-1 or His tagged TIGIT for 5 mins. Dissociation was measured after transfer of the biosensors into kinetic buffer alone and monitoring of the interferometry signal for 10 minutes. The observed on and off rates (K_a and K_d) were fit using a 1:1 binding global fit model comprising at least 5 concentrations tested, followed by calculation of the equilibrium binding constant K_D .

The results of this analysis in FIG. 13A show that the binding affinities of Bi-TPM-94A and Bi-TPM-94B to PD-1 are stronger than the binding affinity of a benchmark anti-PD-1 antibody to PD-1. Likewise, FIG. 13B shows that the binding affinities of Bi-TPM-94A and Bi-TPM-94A to TIGIT are stronger than the binding affinity of a benchmark anti-TIGIT antibody to TIGIT.

A blocking assay using CHO cells stably expressing TIGIT and 1 µg/ml biotinylated PVR-muFc was used to compare Bi-TPM-94A and Bi-TPM-94B ability to block the binding of TIGIT to its PVR ligand TIGIT. Briefly, cells were incubated with biotinylated PVR-Fc and the Bi-TPM molecules, washed and bound PVR-muFc was detected with PE streptavidin using in the iQue Intellicyt system. FIG. 14A shows, both molecules similarly block the binding of TIGIT and PVR. Similarly, both molecules can block the binding of PD-1 to its PD-L1 ligand (FIG. 14B). The results of these assay further revealed that Bi-TPM-94A and Bi-TPM-94B exhibited IC₅₀ values slightly better than corresponding anti-TIGIT and anti-PD-1 benchmark (BM) antibodies.

To determine whether Bi-TPM-94A and Bi-TPM-94B can bind both PD-1 and TIGIT simultaneously, huPD-1-Fc-coated (5 µg/ml) 96 well ELISA plates were blocked with 1% BSA in PBS and incubated for 2 hours with serial dilutions of the anti-PD-1/anti-TIGIT bispecific antibodies, followed by addition and incubation for 2 hours with His-tagged huTIGIT protein. After washing, HRP conjugated anti-His tag Ab and TMB substrate were added as detection agents and quantified with a Perkin Elmer multimode plate reader. The results of this assay in FIG. 15 show simultaneous binding of PD-1 and TIGIT by Bi-TPM-94A and Bi-TPM-94B.

To evaluate the ability of Bi-TPM-94B to induce IFN-γ production, 250,000 human PBMCs from donors screened for CMV antigen reactivity, i.e., Donor 287 (FIG. 16A) and Donor 401 (FIG. 16B) were stimulated with 0.1 µg/ml of CMV-infected cell lysates (lanes 2-7) to stimulate CMV reactive T cells or not stimulated with CMV-infected cell lysates (lane 1). Shp-77 cells were co-cultured with the PBMCs to provide an immune function inhibitory environment and further incubated with human IgG (lane 3), parental anti-TIGIT mAb B21-35 (lane 4), parental anti-PD-1 mAb 2P17 (lane 5), parental anti-TIGIT mAb B21-35 in combination with parental anti-PD-1 mAb 2P17 (lane 6), or Bi-TPM-94B (lane 7). 5 days later, cell culture supernatants were examined for IFN-γ production by ELISA.

The results of this analysis in FIGS. 16A-16B show increased IFN-γ secretion from human PBMCs (Donor 287, FIG. 16A; Donor 401, FIG. 16B) with Bi-TPM-94B relative to the monospecific parental mAbs or the combination of monospecific parental anti-PD-1 and anti-TIGIT antibodies, as well as the negative controls.

To evaluate the ability of Bi-TPM-94B to induce T cell proliferation, 250,000 human PBMCs from the Donor 287 (FIG. 17A) and Donor 401 (FIG. 17B) were stimulated with 0.1 µg/ml of CMV-infected cell lysates for 2 days to stimulate CMV reactive T cells and then labeled with carboxyfluorescein succinimidyl ester (CFSE). The CFSE-labeled PBMCs were then co-cultured with Shp-77 cells to

provide an immune function inhibitory environment and further incubated with human IgG (lane 1), parental anti-TIGIT mAb B21-35 (lane 2), parental anti-PD-1 mAb 2P17 (lane 3), parental anti-TIGIT mAb B21-35 in combination with parental anti-PD-1 mAb 2P17 (lane 4), or Bi-TPM-94B (lane 5). 5 days later, CFSE signal on CD3+ T cells were analyzed with an iQue intellicyt system and a proliferation index was calculated, based on the loss of CFSE signal.

The results of this analysis in FIGS. 17A-17B show that Bi-TPM-94B enhances proliferation of primary human T cells from Donor 287 PBMCs (FIG. 17A) and Donor 401 PBMCs (FIG. 17B) to a greater extent than the individual or combination of parental anti-PD-1 and anti-TIGIT antibodies, as well as the negative controls.

To evaluate the pharmacokinetic properties of Bi-TPM-94A and Bi-TPM-94B in vivo, a pharmacokinetic profile was generated. Briefly, 10 mg/kg of Bi-TMP-94A or Bi-TPM-94B was intravenously injected into the tail vein of 6-10 week old female CD1 mice (n=2 mice). Serum was harvested at 3 minutes, 3 hours, 1 day, 3 days, 7 days and 10 days post injection. To detect the antibodies in the serum, 96 well ELISA plates were coated with 5 µg/ml goat anti-human IgG (Fc specific) F(ab')₂ fragment (Sigma, #SAB3701274) and then blocked with 5% milk in PBS. Following the blocking step, both the mouse serum and purified Bi-TPM-94A or Bi-TPM-94B molecules (as a standards) were serially diluted in 5% milk, and were then added to the plate and incubated for 2 hr. After the incubation, the wells were washed and then incubated with Peroxidase AffiniPure Mouse Anti-Human IgG Fcγ Fragment Specific (Jackson ImmunoResearch #209-035-098) and TMB-ELISA Substrate Solution (Thermo Scientific #34029) and quantified by OD650 signal with a Perkin Elmer multimode plate reader.

The results of this analysis in FIG. 18 showed that the half-life ($T_{1/2}$) of the bispecific antagonist Bi-TPM-94A and Bi-TMP-94B are 7-10 days. Thus, the Bi-TPM-94A and B molecules have the improved property of higher affinity binding as compared to Bi-TPM-93, and Bi-TPM-94B, with the extended G4S linker in the anti-TIGIT scfv, is further improved as compared to Bi-TPM-93 and Bi-TPM-94A with regards to homogeneity.

Example 4: Identification and Functional Characterization of Anti-LAG-3 Monoclonal Antibodies

In another aspect, the present application relates to the screening and characterization of monoclonal antibodies or the antigen-binding portions thereof that specifically bind to the human immune checkpoint regulator, LAG-3. FIG. 19A shows the heavy chain CDR1, CD2 and CDR3 sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A that were isolated. FIG. 19B shows the light chain CDR1, CD2 and CDR3 sequences corresponding to the anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A. FIG. 20 shows the VH and VL sequences of anti-LAG-3 mAbs 2L2A.1, 2L2A.6, 2L27B and 3L1A.

A blocking assay was carried out to show that the mAbs 2L2A and 2L27B (FIG. 21A) and 2L37A and 3L1A (FIG. 21B) to block the interaction between human LAG-3 and its major ligand, major histocompatibility complex II (MHC II) antigen expressed on Raji cells. Briefly, 2-fold serial dilutions of the mAbs 2L2A and 2L27B (FIG. 21A) and 2L37A and 3L1A (FIG. 21B) were prepared. The serial dilutions and human LAG-3-huFc were incubated for 30 mins at room temperature and then added to Raji cells and further incu-

bated for 30 minutes on ice. Then, Raji cells were washed and LAG-3-huFc binding on Raji cells was detected with anti-human IgG PE. Cells were fixed prior to analysis with an iQue Intellicyt system. The results of this analysis in FIGS. 21A-21B confirm the ability of the mouse anti-LAG-3 mAbs to block the interaction between LAG-3 and its major ligand, major histocompatibility complex II (MHC II) antigen to a degree comparable to that of an anti-LAG-3 benchmark (BM) mAb.

The above-described blocking assay was further used to calculate IC₅₀ values reflecting inhibition of binding of LAG-3 to MHC II by anti-LAG-3 antibodies, specifically, a humanized anti-LAG-3 variant, 2L2A.1, an anti-LAG-3 benchmark (BM) antibody (BMS-986016, Bristol-Myers Squibb), and a chimeric 2L2A antibody comprising mouse 2L2A CDRs in a human Ig.

The results of these assay in FIG. 22 show that the humanized anti-LAG-3 mAb 2L2A.1 is a better blocker than the the BM mAb and the chimeric 2L2A antibody comprising mouse 2L2A CDRs in a human Ig as reflected in the lower IC₅₀ value obtained.

To evaluate the binding affinities and kinetics of binding to His tagged human LAG-3 by the anti-LAG-3 mAb 2L2A.1, bio-layer interferometry was carried out using the Octet RED96 system (ForteBio), essentially as described above in Example 3 above with reference to FIGS. 13A-13B as determined by surface plasmon resonance (SPR), along with corresponding binding affinity constants. FIG. 23A shows the binding affinities of the humanized 2L2A.1 antibody to His-tagged human LAG-3. FIG. 23B similarly shows the binding affinity constants for binding of the humanized 2L2A.1 antibody to human LAG-3 fused to mouse IgG2a (huLAG-3-mIgG2a).

To further evaluate the ability of 2L2A.1 to bind human LAG-3, serial dilutions of 2L2A.1 or a LAG-3 benchmark (BM) antibody were added to CHO-K1 cells (20,000 cells/well) expressing human LAG-3. The mixtures were incubated at 4° C. for 20 min, washed 3 times, and stained with the secondary antibody, PE labeled F(ab')₂-Goat anti-human IgG Fc (Thermo Scientific #H10104) by incubation at 4° C. for 20 min. Cells were washed and resuspended in 7AAD solution and fixed in 10% neutral buffered formalin solution for 15 minutes before analysis with the iQue Intellicyt system. Corresponding EC₅₀ values reflecting the half maximal effective concentrations (EC₅₀) producing a response halfway between the baseline and maximum response with respect to binding human LAG-3 were also determined. As shown in FIG. 24, the results show that 2L2A.1 has a higher affinity of binding for human LAG-3 than the BM antibody.

FIG. 25 shows a non-denaturing polyacrylamide gel (PAGE) analysis demonstrating robust expression of humanized anti-LAG-3 mAb variant 2L2A.1 in transiently expressed human embryonic kidney (HEK) 293 cells as compared to a control (ctrl) antibody.

To evaluate whether LAG-3 and PD-1 are coexpressed in activated human CD3+ T cells, FACS analysis was carried out on donor PBMCs activated with anti-human CD3/CD28. The results of this analysis in FIG. 26 confirmed the co-expression of LAG-3 and PD-1 by human PBMCs activated with *Staphylococcal enterotoxin B* (SEB).

To evaluate the ability of 2L2A.1 to induce IFN-γ production, 100,000 human PBMCs from two donors, i.e., Donor 0105 (FIG. 27A) and Donor 0817 (FIG. 27B) were plated on a 96-well ELISA plate. PBMCs were either not stimulated (lane 1) or stimulated with 0.5 µg/ml of *Staphylococcal enterotoxin B* (SEB; lanes 2-4). To the stimulated

cells, Benchmark (BM) anti-LAG-3 mAb (lane 3), the 2L2A.1 mAb (lane 4), or an isotype-matched control antibody (lane 2), were added and incubated at 37° C. for 5 days. Cell culture supernatants were then examined for IFN- γ production by ELISA. The results in FIGS. 27A-27B show increased IFN- γ secretion from both human donor PBMCs with 2L2A.1 relative to the anti-LAG-3 BM.

A similar analysis was done, but also assessed proliferation of the PBMCs with 3 additional donor PBMCs, Donor 223 (FIG. 28A), Donor 224 (FIG. 28B), and Donor 225 (FIG. 28C). The results in FIGS. 28A-28B further establish increased IFN- γ secretion from human donor PBMCs with 2L2A.1 relative to the anti-LAG-3 BM. To assess proliferation, the 3 donor PBMCs were labeled with CFSE, stimulated with 100 ng/ml SEB, and Benchmark (BM) anti-LAG-3 mAb (lane 3), the 2L2A.1 mAb (lane 4), or an isotype-matched control antibody (lane 2), were added. The PBMC mixtures were incubated at 37° C. for 5 days, and loss of CFSE signal on CD4 T cells were quantified by FACS to generate a Proliferation Index. The results shown in FIGS. 29A and 29B establish that 2L2A.1 can induce more primary T cell proliferation than a benchmark (BM) anti-LAG-3 mAb.

Example 5: Design and Functional Characterization of Bispecific Anti-LAG-3/Anti-TIGIT scFv Antagonist

Based on the design and characterization of the bispecific anti-PD-1/anti-TIGIT scFv described in Example 1, it was of interest to evaluate whether the benefits in manufacturability and functionality of this design can be extended to an analogous bispecific anti-LAG-3/anti-TIGIT scFv design. FIGS. 30A-30B depict two exemplary bispecific antitumor antagonists, Bi-LT-1, with the extended scfv linker 4xG4S (FIG. 30A) and Bi-LT-3, with the extended scfv linker 6xG4S (FIG. 30B). FIG. 31 summarizes the arrangement of functional domains in the bispecific antagonists depicted in FIGS. 30A-30B. FIG. 32 show the heavy chain (HC) and light chain (LC) amino acid sequences corresponding to the bispecific antagonists depicted in FIGS. 30A-30B.

To evaluate the ability of the bispecific antitumor antagonists, Bi-LT-1 and Bi-LT-3 to block the interaction between TIGIT and its ligand, human PVR (CD155), and additionally block the interaction between LAG-3 and its major ligand, major histocompatibility complex II (MHC II) antigen, cell-based blocking assays were carried as follows.

Briefly, to show that Bi-LT-1 and Bi-LT-3 can block the interaction between TIGIT and its ligand, human PVR (CD155), a cell-based blocking assay was carried out in which serial dilutions of Bi-LT-1, Bi-LT-3, or Bi-TPM-94B (described in Example 1 above) were incubated with human TIGIT-transfected CHOK1 cells and CD155/PVR-mouse IgG2a for 30 minutes on ice. CD155/PVR-mouse IgG2a binding on CHOK1 cells was detected with anti-mouse IgG PE. Cells were fixed prior to analysis with an iQue intellicyt system. The results from this assay are shown in FIG. 33A and reveal that Bi-LT-1 and Bi-LT-3, with the extended scfv linkers retain their bioactivity for TIGIT.

To show that the bispecific antitumor antagonists, Bi-LT-1 and Bi-LT-3 can also block the interaction between LAG-3 and its major ligand, major histocompatibility complex II (MHC II) antigen a cell-based blocking assay was carried out in which serial dilutions of Bi-LT-1, Bi-LT-3, or an anti-LAG-3 benchmark (BM) antibody were incubated with LAG-3-mouse IgG2a for 30 mins at room temperature, added to Raji cells, and further incubated for 30 minutes on

ice. The Raji cells were then washed, and LAG-3-mouse IgG2a binding on Raji cells was detected with anti-mouse IgG PE. Cells were fixed prior to analysis with an iQue intellicyt system. The results of this assay are shown in FIG. 33B indicate that Bi-LT-1 and Bi-LT-3 retain their bioactivity for LAG-3 similar to the benchmark anti-LAG3 antibody. The assay data was further used to calculate IC50 values (nm) depicted, which are comparable to the IC50 value for the anti-LAG-3 benchmark (BM) antibody. Taken together, the results in FIGS. 33A and 33B establish that Bi-LT-1 and Bi-LT-3 retain their bioactivity for both TIGIT and LAG-3.

To see whether Bi-LT-1 and Bi-LT-3 can simultaneously bind both LAG-3 and TIGIT, 5 μ g/ml LAG-3-mIgG was coated on an ELISA plate at 4° C. overnight and then blocked before adding serial dilutions of LT-1, LT-3 or a parental LAG-3 mAb. Following a 1 hr incubation at room temperature, the plate was washed and 500 ng/ml His tagged HuTIGIT was added and incubated for 1 hr at room temperature. Plate bound His tagged HuTIGIT was then detected using anti-His tag HRP and a TMB substrate. This results of this assay in FIG. 34 demonstrate that Bi-LT-1 and Bi-LT-3 can simultaneously bind both LAG-3 and TIGIT.

FIGS. 35A-35D depict pharmacokinetic profiles and in vivo half-lives ($T_{1/2}$) corresponding to the parental anti-LAG-3 mAb (FIG. 35A), an anti-LAG-3 benchmark mAb (FIG. 35B), Bi-LT-1 (FIG. 35C), or Bi-LT-3 (FIG. 35D) following a tail vein injection into 6-10 week old female CD1 mice. The antibodies and bispecific antagonists were recovered from serum taken at various times post-injection and subjected to analysis by ELISA. The results indicate both Bi-LT-1 and Bi-LT-3 have similar pharmacokinetics as compared to the anti-LAG3 parental antibody and to the benchmark antibody, with half-lives ($T_{1/2}$) of 5-6 days.

To evaluate species homogeneity and stability of protein A purified Bi-LT-1 and Bi-LT-3, a size exclusion chromatography (SEC) profile of Bi-LT-1 and Bi-LT-3 was generated as described above. The results of this analysis in FIG. 36A are consistent with both of the extended scfv linkers creating species homogeneity and good stability after 7 days at 4° C. FIG. 36B shows a size-exclusion ultra-high performance liquid chromatography (SE-UHPLC) analysis carried out as described above. The results from this analysis are consistent with the species homogeneity observed in FIG. 36A, as reflected in low levels of high molecular weight (HMW) species at Day 0 and Day 7 (1.3%, 1.5%, respectively for Bi-LT-1 and 1.3%, 1.4%, respectively for Bi-LT-3) and low molecular weight (LMW) species at Day 0 and Day 7 (0.2%, 0.2%, respectively, for Bi-LT-1 and 0.3%, 0.5%, respectively for Bi-LT-3) in comparison to dimer species at Day 0 and Day 7 (98.4%, 98.3%, respectively for Bi-LT-1 and 98.4%, 98.1%, respectively for Bi-LT-3).

To evaluate the ability of Bi-LT-1 and Bi-LT-3 to induce IFN- γ production, human PBMCs were stimulated with 100 ng/ml SEB in the presence of either SHP-77 cells (FIG. 37A) or H358 cells (FIG. 37B) to provide an immune suppressive signal. Human IgG control (lane 3), anti-TIGIT mAb (B21-35) alone (lane 4), anti-LAG-3 mAb alone (lane 5), a combination of anti-TIGIT mAb and anti-LAG-3 mAb (lane 6), Bi-LT-1 (lane 7), or Bi-LT-3 (lane 8) were then added to rescue T cell function (FIGS. 37A, 37B). 4 days later, cell culture supernatants were collected and examined for IFN- γ level by ELISA. The results of these analyses in FIGS. 37A and 37B show that LT-1 and LT-3 are more potent than the combination of parental TIGIT and LAG-3 antibodies.

FIG. 38 shows an evaluation of the ability of Bi-LT-1 and Bi-LT-3 to induce proliferation of CD4 T cells. Human

PMBC were labeled with CFSE and then stimulated with 100 ng/ml SEB, in the presence of SHP-77 cells to provide immune suppressive signal. 128 nM human IgG control (lane 3), anti-TIGIT mAb B21-35 (lane 4), anti-LAG-3 mAb (lane 5), the combination of anti-TIGIT mAb and anti-LAG-3 mAb (lane 6), Bi-LT-1 (lane 7) or Bi-LT-3 (lane 8) were used to rescue T cell function. 5 days later, loss of CFSE signal on CD4 T cells was quantified by FACS to determine the Proliferation Index. Similar to the increased stimulation of IFN γ over the parental antibodies and the combination of the 2 parental antibodies, both Bi-LT-1 and Bi-LT-3 have increased ability to stimulate proliferation of human CD4 T cells.

The above description is for the purpose of teaching a person of ordinary skill in the art how to practice the present invention and is not intended to detail all those obvious modifications and variations which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

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35 40 45
Ile Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Gly Tyr Asn Pro Ser Leu
50 55 60
Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80
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35 40 45
Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln
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Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp														
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Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser														
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Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Ser Cys														
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Thr	Ile	His	Trp	Val	Gln	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
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	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Thr	Ser	Thr	Asp	Thr	Ala	Tyr
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Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
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Ala	Thr	Gly	Met	Leu	Arg	Trp	Phe	Ala	Asp	Trp	Gly	Gln	Gly	Thr	Leu
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Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Thr	Pro	Leu
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			20					25					30		
Thr	Ile	His	Trp	Val	Gln	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
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Gly	Tyr	Ile	Tyr	Pro	Arg	Asp	Gly	Ser	Ser	Lys	Tyr	Asn	Val	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Thr	Ser	Thr	Asp	Thr	Ala	Tyr
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Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
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Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
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Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
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Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Ser	Thr	Pro	Leu
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Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Val	Ser	Ser	Asp
			20					25					30		
Tyr	Ala	Trp	Asn	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp
			35				40					45			
Ile	Gly	Tyr	Ile	Thr	Tyr	Ser	Gly	Ser	Thr	Ser	Tyr	Asn	Pro	Ser	Leu
			50				55					60			
Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser
65					70					75					80
Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Arg	Gln	Val	Gly	Leu	Gly	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ala										
			115												

<210> SEQ ID NO 59
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Val	Ser	Thr	Ala
			20					25					30		
Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40					45			
Tyr	Ser	Ala	Ser	Tyr	His	Tyr	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50				55					60			

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
          85          90          95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
          100          105

<210> SEQ ID NO 60
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 60

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Asp
1          5          10          15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Thr Ser Asp
          20          25          30

Ser Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
          35          40          45

Ile Gly Tyr Ile Thr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
          50          55          60

Arg Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65          70          75          80

Leu Lys Leu Ser Ser Val Thr Ala Val Asp Thr Ala Val Tyr Tyr Cys
          85          90          95

Thr Arg Arg Gln Val Gly Leu Gly Phe Ala Tyr Trp Gly Gln Gly Thr
          100          105          110

Leu Val Thr Val Ser Ala
          115

<210> SEQ ID NO 61
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1          5          10          15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
          20          25          30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35          40          45

Tyr Ser Ala Ser Tyr Arg Phe Thr Gly Ala Pro Ser Arg Phe Ser Gly
          50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Gly Ile Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Trp
          85          90          95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Phe Lys
          100          105

<210> SEQ ID NO 62
<211> LENGTH: 121
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 62															
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ser	Glu	Leu	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
			20					25					30		
Gly	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Trp	Ile	Asn	Thr	Tyr	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe
	50					55					60				
Lys	Gly	Arg	Phe	Val	Phe	Ser	Leu	Asp	Thr	Ser	Val	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Ile	Ser	Ser	Leu	Lys	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Ala	Pro	Pro	Tyr	Gly	Tyr	Asp	Val	Arg	Phe	Ala	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
	115						120								
<210> SEQ ID NO 63															
<211> LENGTH: 112															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 63															
Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Leu	Gly
1				5					10					15	
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Ile	Val	His	Ser
			20					25					30		
Asn	Gly	Asn	Thr	Tyr	Leu	Glu	Trp	Phe	Gln	Gln	Arg	Pro	Gly	Gln	Ser
	35						40					45			
Pro	Arg	Val	Leu	Ile	Tyr	Lys	Val	Ser	Asp	Arg	Phe	Ser	Gly	Val	Pro
	50					55					60				
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70					75					80
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Phe	Gln	Gly
			85						90					95	
Ser	His	Val	Pro	Trp	Thr	Phe	Gly	Arg	Gly	Thr	Lys	Leu	Glu	Ile	Lys
		100						105					110		
<210> SEQ ID NO 64															
<211> LENGTH: 121															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 64															
Gln	Val	Thr	Leu	Lys	Glu	Ser	Gly	Pro	Thr	Leu	Val	Lys	Pro	Thr	Gln
1				5					10					15	
Thr	Leu	Thr	Leu	Thr	Cys	Thr	Phe	Ser	Gly	Phe	Ser	Leu	Ser	Thr	Phe
			20					25					30		
Ala	Met	Gly	Val	Gly	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Ala	Leu	Glu
		35					40					45			

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Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Met Asp Tyr Ser Tyr Phe Ala Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 65
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Leu Phe Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Asn Arg Ala Pro Trp Val Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
85 90 95

His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 66
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Arg Thr Ser Tyr Ala Gln Met Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Arg Thr Thr Tyr Ser Met Asp Tyr
1 5

Thr Tyr Tyr Ile Tyr
1 5

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<210> SEQ ID NO 77
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

Gly Ile Asn Pro Gly Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe Lys
1 5 10 15

Ile

<210> SEQ ID NO 78
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 78

Arg Tyr His Gly Tyr Asp Gly Gly Leu Asp Tyr
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

Ser Tyr Tyr Ile His
1 5

<210> SEQ ID NO 80
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80

Trp Ile Phe Pro Gly Ser Gly Asn Ser Lys Tyr Asn Glu Asn Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 81
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81

Ser Glu Thr Tyr Asp Tyr Gly Asp Tyr
1 5

<210> SEQ ID NO 82
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

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<210> SEQ ID NO 83
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 83

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<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 84

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<210> SEQ ID NO 85
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 85

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<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 86

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<210> SEQ ID NO 87
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 87

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<210> SEQ ID NO 88
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 88

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<210> SEQ ID NO 89
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 89

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<210> SEQ ID NO 90
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 90

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<210> SEQ ID NO 91
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 91

```
<210> SEQ ID NO 92
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 92

```
<210> SEQ ID NO 93
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 93

```
<210> SEQ ID NO 94
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 94																			
Ser	Ala	Ser	Tyr	Arg	Tyr	Ser													
1					5														
<210> SEQ ID NO 95																			
<211> LENGTH: 9																			
<212> TYPE: PRT																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 95																			
Gln	Gln	Tyr	Tyr	Ser	Tyr	Pro	Tyr	Thr											
1				5															
<210> SEQ ID NO 96																			
<211> LENGTH: 117																			
<212> TYPE: PRT																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 96																			
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly				
1				5					10					15					
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Phe				
			20					25					30						
Leu	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val				
	35						40					45							
Ser	Thr	Ile	Ser	Gly	Gly	Gly	Arg	Asp	Thr	Tyr	Tyr	Val	Asp	Ser	Val				
	50					55					60								
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr				
65					70				75					80					
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
			85						90					95					
Ala	Lys	Arg	Thr	Thr	Tyr	Ser	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser				
			100					105					110						
Val	Thr	Val	Ser	Ser															
			115																
<210> SEQ ID NO 97																			
<211> LENGTH: 107																			
<212> TYPE: PRT																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 97																			
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly				
1				5					10					15					
Asp	Arg	Val	Thr	Ile	Thr	Cys	Leu	Ala	Ser	Gln	Thr	Ile	Gly	Thr	Trp				
			20					25					30						
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile				
		35					40					45							
Tyr	Ala	Ala	Thr	Ser	Leu	Ala	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly				
	50					55				60									
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro				
65					70					75				80					

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<210> SEQ ID NO 100
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 100

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1			5						10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Asp	Tyr	Thr	Phe	Thr	Asn	Ser
		20					25					30			
Tyr	Ile	Tyr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40						45			
Gly	Gly	Ile	Asn	Pro	Ser	Asn	Gly	Gly	Thr	Asn	Phe	Asn	Glu	Lys	Phe
	50					55				60					
Lys	Thr	Arg	Val	Thr	Ser	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
65					70				75					80	
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Val	Val	Tyr	Tyr	Cys
			85					90					95		
Ala	Arg	Arg	Asp	Tyr	Arg	Tyr	Asp	Gly	Gly	Phe	Asp	Ser	Trp	Gly	Gln
			100				105						110		
Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser								
	115					120									

<210> SEQ ID NO 101
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Ser	Ala	Ser	Ser	Ser	Leu	Tyr	Ser	Ser
		20					25					30			
Tyr	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu
	35					40					45				
Ile	Tyr	Arg	Ala	Ser	Phe	Leu	Ala	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser
	50				55					60					
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln
65				70				75						80	
Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Ser	Ser	Ile	Pro
			85					90						95	
Leu	Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Asp	Leu	Lys				
		100					105								

<210> SEQ ID NO 102
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 102

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1			5						10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Asp	Tyr	Thr	Phe	Thr	Asn	Ser
		20					25					30			
Tyr	Ile	Tyr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40						45			
Gly	Gly	Ile	Asn	Pro	Ser	Asn	Gly	Gly	Thr	Asn	Phe	Asn	Glu	Lys	Phe
	50					55				60					

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<210> SEQ ID NO 105														
<211> LENGTH: 111														
<212> TYPE: PRT														
<213> ORGANISM: Artificial Sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 105														
Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ala	Val	Ser	Pro Gly
1				5					10				15	
Gln	Arg	Ala	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr Ser
			20					25					30	
Gly	Phe	Ser	Tyr	Ile	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro Pro
			35				40					45		
Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Leu	Glu	Ser	Gly	Val	Pro Ala
			50			55					60			
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile Asn
65					70				75					80
Pro	Val	Glu	Ala	Asn	Asp	Thr	Ala	Asn	Tyr	Tyr	Cys	Gln	His	Thr Trp
				85					90					95
Glu	Leu	Pro	Asn	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100					105					110	
<210> SEQ ID NO 106														
<211> LENGTH: 117														
<212> TYPE: PRT														
<213> ORGANISM: Artificial Sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 106														
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly Ala
1				5					10					15
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser Tyr
			20					25					30	
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp Met
			35				40					45		
Gly	Trp	Ile	Phe	Pro	Gly	Ser	Gly	Asn	Ser	Lys	Tyr	Asn	Glu	Asn Phe
			50				55					60		
Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Val Tyr
65					70				75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr Cys
				85					90					95
Ala	Ser	Glu	Thr	Tyr	Asp	Tyr	Gly	Asp	Tyr	Trp	Gly	Gln	Gly	Thr Leu
			100					105					110	
Val	Thr	Val	Ser	Ser										
				115										
<210> SEQ ID NO 107														
<211> LENGTH: 107														
<212> TYPE: PRT														
<213> ORGANISM: Artificial Sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 107														
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Phe	Leu	Ser	Ala	Ser	Val Gly
1				5					10					15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asn	Val	Gly	Thr Asn
			20					25					30	

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<210> SEQ ID NO 112
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 112

Ser

<210> SEO ID NO 113

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<211> LENGTH: 12
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<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

<210> SEO ID NO 114

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<211> LENGTH: 17
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<211> LENGTH: 1
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

Ser

<210> SEO ID NO 115

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<211> LENGTH: 12
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<211> LENGTH: 12
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

<210> SEO ID NO 116

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<211> LENGTH: 17
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<211> LENGTH: 1
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 116

Ser

<210> SEO ID NO 117

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<211> SEQ ID NO
<211> LENGTH: 6
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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

(400) SEQUENCE: 117

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 118

Tyr Ile Ser Asp Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu Lys Ser
1             5             10            15

```

```
<210> SEQ ID NO 119
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 119

Ser Phe Leu Arg Leu Arg Ser Tyr Phe Asp His
1 5 10

```
<210> SEQ ID NO 120
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 120

Ser Tyr Gly Ile Asn
1 5

```
<210> SEQ ID NO 121
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 121

Cys Ile Tyr Ile Gly Asn Asp Tyr Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

```
<210> SEQ ID NO 122
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 122

Ala Tyr Tyr Gly Ser Arg Val Asp Tyr
1 5

```
<210> SEQ ID NO 123
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 123

Arg Ala Ser Gln Asp Ile Asp Asn Tyr Leu Asn
1 5 10

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<210> SEQ ID NO 124
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 124

Tyr Thr Ser Arg Leu His Ser
1 5

<210> SEQ ID NO 125
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 125

Gln Gln Gly Tyr Thr Leu Pro Trp Thr
1 5

<210> SEQ ID NO 126
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 126

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 127

Tyr Thr Ser Arg Leu Gln Ser
1 5

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

Gln Gln Gly Asn Thr Leu Pro Trp Thr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129

Gln Gln Gly Asp Thr Leu Pro Trp Thr
1 5

<210> SEQ ID NO 130

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<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

Lys Ala Ser Gln Asp Val Asn Val Ala Val Ala
1 5 10

<210> SEQ ID NO 131
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

Trp Ala Ser Thr Arg His Ile
1 5

<210> SEQ ID NO 132
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

Gln Gln His Tyr Ser Thr Pro Tyr Thr
1 5

<210> SEQ ID NO 133
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 133

Lys Ala Ser Gln Asp Ile Asn Lys Tyr Ile Ala
1 5 10

<210> SEQ ID NO 134
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 134

Tyr Thr Ser Thr Leu Gln Pro
1 5

<210> SEQ ID NO 135
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 135

Leu Gln Tyr Asp Asn Leu Tyr Thr
1 5

<210> SEQ ID NO 136
<211> LENGTH: 8

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 136

Gln Ser Ile Ser Asp Tyr Leu His
1 5

<210> SEQ ID NO 137
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 137

Cys Ala Ser Gln Ser Ile Ser Gly
1 5

<210> SEQ ID NO 138
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 138

Gln Asn Gly His Ser Phe Pro Tyr Thr
1 5

<210> SEQ ID NO 139
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 139

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Met His Trp Met Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Asn Thr Asn Asn Tyr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Ser Arg Val Thr Ser Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Val Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Asp Tyr Gly Ser Ser Pro Tyr Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 140
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 140

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Asp	Asn	Tyr
		20					25				30				
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35					40				45					
Lys	Tyr	Thr	Ser	Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55				60						
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70					75					80	
Glu	Asp	Phe	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Tyr	Thr	Leu	Pro	Trp
			85					90					95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100						105							

<210> SEQ ID NO 141
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
		20					25				30				
Trp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40					45				
Gly	Met	Ile	His	Pro	Asn	Val	Gly	Ser	Thr	Asn	Tyr	Asn	Glu	Lys	Phe
	50				55				60						
Lys	Ser	Lys	Ala	Thr	Met	Thr	Arg	Asp	Lys	Ser	Ser	Ser	Thr	Val	Tyr
65				70					75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90					95		
Ala	Arg	Ser	Arg	Tyr	Gly	Ser	Ser	Pro	Tyr	Tyr	Phe	Asp	Tyr	Trp	Gly
		100						105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

<210> SEQ ID NO 142
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr
		20					25				30				
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35					40				45					
Tyr	Tyr	Thr	Ser	Arg	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55				60						

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Trp
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

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<210> SEQ ID NO 143
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 143

Gln 1	Val	Gln	Leu 5	Val	Gln	Ser	Gly	Ala	Glu 10	Val	Lys	Lys	Pro	Gly 15	Ala
Ser	Val	Lys 20	Val	Ser	Cys	Lys	Ala	Ser 25	Gly	Tyr	Thr	Phe	Thr 30	Ser	Tyr
Trp	Met	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Met
Gly 50	Met	Ile	His	Pro	Asn	Ser 55	Gly	Gly	Asn	Asn	Tyr 60	Asn	Glu	Lys	Phe
Lys 65	Ser	Arg	Val	Thr	Met 70	Thr	Arg	Asp	Thr	Ser 75	Ile	Ser	Thr	Ala	Tyr 80
Met	Glu	Leu	Ser	Arg 85	Leu	Arg	Ser	Asp	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Arg	Ser	Trp 100	Tyr	Gly	Ser	Ser	Pro 105	Tyr	Tyr	Phe	Asp	Tyr 110	Trp	Gly
Gln	Gly 115	Thr	Leu	Val	Thr	Val	Ser 120	Ser							

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<210> SEQ ID NO 144
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 144

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr
			20					25					30		
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Tyr	Thr	Ser	Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Trp
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

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<210> SEQ ID NO 145
<211> LENGTH: 121
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 145													
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala													
1			5					10				15	
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr													
			20				25				30		
Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met													
		35				40				45			
Gly Met Ile His Pro Thr Gly Val Ser Thr Asp Tyr Asn Glu Lys Phe													
50					55				60				
Lys Ser Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr													
65				70				75				80	
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys													
			85				90					95	
Ala Arg Ser Asp Tyr Gly Ser Ser Pro Tyr Tyr Phe Asp Tyr Trp Gly													
		100				105				110			
Gln Gly Thr Leu Val Thr Val Ser Ser													
		115				120							
<210> SEQ ID NO 146													
<211> LENGTH: 107													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 146													
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly													
1			5					10				15	
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr													
		20				25				30			
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile													
		35			40					45			
Lys Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly													
50				55				60					
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro													
65			70					75				80	
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Thr Leu Pro Trp													
		85				90						95	
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys													
		100				105							
<210> SEQ ID NO 147													
<211> LENGTH: 120													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 147													
Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln													
1			5					10				15	
Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp													
		20				25				30			
Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp													
		35			40					45			

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Met Gly Tyr Ile Ser Asp Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Asn Ser Phe Leu Arg Leu Arg Ser Tyr Phe Asp His Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> SEQ ID NO 148
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 148

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Val Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Phe Trp Ala Ser Thr Arg His Ile Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 149
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 149

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Trp Cys Ile Tyr Ile Gly Asn Asp Tyr Thr Asn Tyr Asn Glu Lys
50 55 60

Phe Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95

```
<210> SEQ ID NO 152
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 152

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Val	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Gln	Ser	Ile	Ser	Asp	Tyr	Leu	His	Trp
			20					25					30		
Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	Lys	Cys	Ala
			35					40				45			
Ser	Gln	Ser	Ile	Ser	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser
			50					55				60			
Gly	Ser	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro	Glu	Asp	Phe
65					70					75					80
Ala	Val	Tyr	Tyr	Cys	Gln	Asn	Gly	His	Ser	Phe	Pro	Tyr	Thr	Phe	Gly
				85					90					95	
Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys								
			100												

<210> SEQ ID NO 153
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Trp	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35				40					45			
Gly	Met	Ile	His	Pro	Asn	Ser	Gly	Gly	Asn	Asn	Tyr	Asn	Glu	Lys	Phe
			50				55				60				
Lys	Ser	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85				90						95	
Ala	Arg	Ser	Trp	Tyr	Gly	Ser	Ser	Pro	Tyr	Tyr	Phe	Asp	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115				120								

<210> SEQ ID NO 154
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Asp	Asn	Tyr
			20					25					30		
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40					45			
Lys	Tyr	Thr	Ser	Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50				55				60				

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Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Phe	Cys	Gln	Gln	Gly	Tyr	Thr	Leu	Pro	Trp
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							
<210> SEQ ID NO 155															
<211> LENGTH: 327															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 155															
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
65					70					75					80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
				85					90					95	
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro
			100					105					110		
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
		115					120					125			
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
	130					135					140				
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
145					150					155					160
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
				165					170					175	
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
		180						185					190		
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
		195					200					205			
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
		210				215						220			
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
225					230					235					240
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
				245					250					255	
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
		260						265					270		
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
		275					280					285			
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
	290					295					300				
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
305					310					315					320

Leu Ser Leu Ser Leu Gly Lys
325

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<210> SEQ ID NO 156
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 156

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
145					150					155					160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

<210> SEQ ID NO 157

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<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 157

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
325 330

<210> SEQ ID NO 158
<211> LENGTH: 698
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 158

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly		
1				5					10					15			
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Phe		
			20					25					30				
Leu	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ser	Thr	Ile	Ser	Gly	Gly	Gly	Arg	Asp	Thr	Tyr	Tyr	Val	Asp	Ser	Val		
	50					55					60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr		
65					70					75					80		
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85						90						95		
Ala	Lys	Arg	Thr	Thr	Tyr	Ser	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser		
			100					105					110				
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu		
		115					120					125					
Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys		
		130				135					140						
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser		
145					150					155					160		
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser		
				165					170					175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser		
		180						185					190				
Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn		
		195					200					205					
Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro		
		210				215					220						
Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe		
225					230					235					240		
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val		
			245						250					255			
Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe		
		260						265					270				
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro		
		275					280					285					
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr		
		290				295					300						
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val		
305					310					315					320		
Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala		
				325					330					335			
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln		
			340					345					350				
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly		
		355					360					365					
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro		
		370				375					380						
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser		
385					390					395					400		
Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu		
				405					410					415			

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Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	
			420					425						430		
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Gly	Gly	Gly	
			435					440						445		
Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	
			450					455						460		
Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	
465						470					475					480
Tyr	Thr	Phe	Thr	Ser	Tyr	Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	
				485					490						495	
Gln	Gly	Leu	Glu	Trp	Met	Gly	Ile	Ile	Asn	Pro	Ser	Gly	Gly	Arg	Thr	
				500				505							510	
Ser	Tyr	Ala	Gln	Met	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	
			515					520						525		
Ser	Thr	Ser	Thr	Val	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	
			530					535						540		
Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Glu	Glu	Gln	Trp	Pro	Val	
545						550						555				560
Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	
				565						570					575	
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	
				580					585						590	
Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	
				595				600						605		
Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Arg	Arg	Tyr	Leu	
						615						620				
Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	
625						630					635					640
Ser	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	
				645						650					655	
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	
				660					665					670		
Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ile	Ile	Pro	Pro	Thr	
				675					680				685			
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys							
				690					695							
<210> SEQ ID NO 159																
<211> LENGTH: 214																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 159																
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly	
1				5					10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Leu	Ala	Ser	Gln	Thr	Ile	Gly	Thr	Trp	
				20				25						30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	
				35				40					45			
Asp	Ala	Ala	Thr	Ser	Leu	Ala	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
				50			55				60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
65					70					75					80	

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Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Phe	Tyr	Ser	Ile	Pro	Trp	
				85					90					95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	
			100					105					110			
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
		115					120					125				
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
	130					135					140					
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
145					150					155					160	
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
				165					170					175		
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	
		180						185					190			
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	
		195					200					205				
Phe	Asn	Arg	Gly	Glu	Cys											
	210															
<210> SEQ ID NO 160																
<211> LENGTH: 698																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 160																
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	
1				5					10					15		
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	
			20					25					30			
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
	35					40						45				
Gly	Trp	Ile	Phe	Pro	Gly	Ser	Gly	Asn	Ser	Lys	Tyr	Asn	Glu	Asn	Phe	
	50					55					60					
Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	
65					70				75						80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ala	Ser	Glu	Thr	Tyr	Asp	Tyr	Gly	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	
			100					105					110			
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
		115					120					125				
Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	
	130					135					140					
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
145					150					155					160	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
			165					170						175		
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
		180						185					190			
Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	
	195						200					205				
Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	
	210					215					220					

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Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	225	230	235	240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	245	250	255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	260	265	270	
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	275	280	285	
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	290	295	300	
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	305	310	315	320
Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	325	330	335	
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	340	345	350	
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	355	360	365	
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	370	375	380	
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	385	390	395	400
Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	405	410	415	
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	420	425	430	
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Gly	Gly	Gly	435	440	445	
Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	450	455	460	
Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	465	470	475	480
Tyr	Thr	Phe	Thr	Ser	Tyr	Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	485	490	495	
Gln	Gly	Leu	Glu	Trp	Met	Gly	Ile	Ile	Asn	Pro	Ser	Gly	Gly	Arg	Thr	500	505	510	
Ser	Tyr	Ala	Gln	Met	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	515	520	525	
Ser	Thr	Ser	Thr	Val	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	530	535	540	
Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Glu	Glu	Gln	Trp	Pro	Val	545	550	555	560
Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	565	570	575	
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	580	585	590	
Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	595	600	605	
Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Arg	Arg	Tyr	Leu	610	615	620	
Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	625	630	635	640

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Ser	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	
			645						650					655		
Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	
			660					665					670			
Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ile	Ile	Pro	Pro	Thr	
		675					680					685				
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys							
	690					695										
<210> SEQ ID NO 161																
<211> LENGTH: 214																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
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<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 161																
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Phe	Leu	Ser	Ala	Ser	Val	Gly	
1				5					10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asn	Val	Gly	Thr	Asn	
		20					25					30				
Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ala	Leu	Ile	
		35				40						45				
Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
	50					55				60						
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
65				70					75					80		
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Tyr	Ser	Tyr	Pro	Tyr	
			85					90						95		
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	
		100						105					110			
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
		115				120						125				
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
	130					135					140					
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
145				150					155						160	
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
			165					170						175		
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	
		180					185						190			
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	
		195					200					205				
Phe	Asn	Arg	Gly	Glu	Cys											
	210															
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<211> LENGTH: 713																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 162																
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	
1				5					10					15		
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	
		20					25					30				

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Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
		35					40					45				
Gly	Trp	Ile	Phe	Pro	Gly	Ser	Gly	Asn	Ser	Lys	Tyr	Asn	Glu	Asn	Phe	
	50					55					60					
Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	
65					70				75						80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Ala	Ser	Glu	Thr	Tyr	Asp	Tyr	Gly	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	
			100					105					110			
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
		115					120					125				
Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	
	130					135					140					
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
145					150					155					160	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
				165					170					175		
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
		180						185					190			
Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	
		195					200					205				
Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	
	210					215					220					
Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	
225					230					235					240	
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	
				245					250					255		
Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	
		260						265					270			
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	
		275					280					285				
Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	
	290					295					300					
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	
305					310					315					320	
Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	
				325					330					335		
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	
			340					345					350			
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	
		355					360					365				
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	
	370					375					380					
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	
385					390					395					400	
Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	
				405					410					415		
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	
		420						425					430			
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Gly	Gly	Gly	
		435					440						445			

Ser	Gly 450	Gly	Gly	Gly	Ser	Gln 455	Val	Gln	Leu	Val	Gln 460	Ser	Gly	Ala	Glu
Val 465	Lys	Lys	Pro	Gly	Ala 470	Ser	Val	Lys	Val	Ser 475	Cys	Lys	Ala	Ser	Gly 480
Tyr	Thr	Phe	Thr	Ser 485	Tyr	Tyr	Met	His	Trp 490	Val	Arg	Gln	Ala	Pro 495	Gly
Gln	Gly	Leu	Glu 500	Trp	Met	Gly	Ile	Ile 505	Asn	Pro	Ser	Gly	Gly	Arg	Thr
Ser	Tyr	Ala 515	Gln	Met	Phe	Gln	Gly 520	Arg	Val	Thr	Met	Thr 525	Arg	Asp	Thr
Ser 530	Thr	Ser	Thr	Val	Tyr	Met 535	Glu	Leu	Ser	Ser	Leu 540	Arg	Ser	Glu	Asp
Thr 545	Ala	Val	Tyr	Tyr	Cys 550	Ala	Arg	Asp	Arg	Glu 555	Glu	Gln	Trp	Pro	Val 560
Gly	Gly	Phe	Asp 565	Tyr	Trp	Gly	Gln	Gly	Thr 570	Leu	Val	Thr	Val	Ser 575	Ser
Gly	Gly	Gly	Gly 580	Ser	Gly	Gly	Gly	Gly 585	Ser	Gly	Gly	Gly	Gly	Ser 590	Gly
Gly	Gly	Gly 595	Ser	Gly	Gly	Gly	Gly 600	Ser	Gly	Gly	Gly	Gly 605	Ser	Asp	Ile
Gln 610	Met	Thr	Gln	Ser	Pro	Ser 615	Ser	Leu	Ser	Ala	Ser 620	Val	Gly	Asp	Arg
Val 625	Thr	Ile	Thr	Cys 630	Arg	Ala	Ser	Gln	Ser	Ile 635	Arg	Arg	Tyr	Leu	Asn 640
Trp	Tyr	Gln	Gln	Lys 645	Pro	Gly	Lys	Ala	Pro 650	Lys	Leu	Leu	Ile	Tyr 655	Ser
Ala	Ser	Asn 660	Leu	Gln	Ser	Gly	Val	Pro 665	Ser	Arg	Phe	Ser	Gly 670	Ser	Gly
Ser	Gly	Thr 675	Asp	Phe	Thr	Leu	Thr 680	Ile	Ser	Ser	Leu	Gln 685	Pro	Glu	Asp
Phe 690	Ala	Thr	Tyr	Tyr	Cys	Gln 695	Gln	Ser	Tyr	Ile	Ile 700	Pro	Pro	Thr	Phe
Gly 705	Gln	Gly	Thr	Lys 710	Val	Glu	Ile	Lys							

Gly

<210> SEQ ID NO 165
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

Asp Asp Gly Tyr Tyr Val His Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 166
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

His Tyr Tyr Met Asn
1 5

<210> SEQ ID NO 167
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167

Leu Ile Asn Pro Tyr Asn Gly Asp Thr Ala Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> SEQ ID NO 168
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

Thr Arg Asp Asp Gly Tyr Tyr Val Glu His
1 5 10

<210> SEQ ID NO 169
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169

Thr Ala Tyr Thr Ile His
1 5

<210> SEQ ID NO 170
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 170

Asp

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<210> SEQ ID NO 171
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 171

His Glu Asp Trp Gly Pro Leu Asp Tyr
1 5

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<210> SEQ ID NO 172
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 172

Arg Ala Ser Gln Asp Ile Ser Ser Arg Leu Thr
1 5 10

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<210> SEQ ID NO 173
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 173

Ala Thr Ser Ser Leu Asp Ser
1 5

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<210> SEQ ID NO 174
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 174

Leu Gln Tyr Ala Ser Ser Pro Leu Thr
1 5

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<210> SEQ ID NO 175
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 175

Arg Ala Ser Gln Asp Ile Gly Ser Arg Leu Asn
1 5 10

```
<210> SEQ ID NO 176
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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Gly Thr Leu Val Thr Val Ser Ser
115 120

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<210> SEQ ID NO 181
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 181

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Arg
20 25 30

Leu Thr Trp Leu Gln Gln Glu Pro Glu Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Thr Ser Ser Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Ser Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 182
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 182

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asn Pro Tyr Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Asp Gly Tyr Tyr Val His Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 183
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 183

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

-continued

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Ser	Arg
		20						25					30		
Leu	Thr	Trp	Leu	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
		35					40					45			
Tyr	Ala	Thr	Ser	Ser	Leu	Asp	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Tyr	Ala	Ser	Ser	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100						105							
<210> SEQ ID NO 184															
<211> LENGTH: 132															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 184															
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	Ser	His	Tyr
			20					25					30		
Tyr	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40						45			
Gly	Leu	Ile	Asn	Pro	Tyr	Asn	Gly	Asp	Thr	Ala	Tyr	Asn	Gln	Lys	Phe
	50					55				60					
Lys	Asp	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
65					70				75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys
			85					90					95		
Thr	Arg	Asp	Asp	Gly	Tyr	Tyr	Val	Glu	His	Phe	Asp	Tyr	Trp	Asp	Asp
			100					105					110		
Gly	Tyr	Tyr	Val	Glu	His	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
		115					120					125			
Thr	Val	Ser	Ser												
		130													
<210> SEQ ID NO 185															
<211> LENGTH: 107															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 185															
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Gly	Ser	Arg
		20						25					30		
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
		35					40					45			
Tyr	Ala	Thr	Ser	Ser	Leu	Asp	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	

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<210> SEQ ID NO 188
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 188

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 189
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> SEQ ID NO 190
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> SEQ ID NO 191
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 191

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> SEQ ID NO 192
<211> LENGTH: 706
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 192

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Met Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asn Pro Tyr Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

-continued

Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85					90					95		
Val	Arg	Asp	Asp	Gly	Tyr	Tyr	Val	His	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	
			100					105					110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
		115					120					125				
Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	
	130						135				140					
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
145					150					155					160	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
				165					170					175		
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
			180					185					190			
Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	
	210					215						220				
Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	
225					230					235					240	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
				245					250					255		
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	
			260					265					270			
Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
		275					280					285				
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
	290					295					300					
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305					310					315					320	
Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	
				325					330					335		
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
			340					345					350			
Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
		355					360					365				
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
	370					375					380					
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	
385					390					395					400	
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	
				405					410					415		
Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	
			420					425					430			
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	
		435					440					445				
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	
		450					455				460					
Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	
465					470					475					480	
Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	Tyr	Met	His	Trp	Val	Arg	Gln	
				485					490					495		

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Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	Gly	Ile	Ile	Asn	Pro	Ser	Gly		
			500					505					510				
Gly	Arg	Thr	Ser	Tyr	Ala	Gln	Met	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr		
		515					520					525					
Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg		
	530						535					540					
Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Glu	Glu	Gln		
545					550					555					560		
Trp	Pro	Val	Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr		
				565					570					575			
Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly		
			580					585					590				
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser		
		595					600					605					
Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala		
	610						615					620					
Ser	Gln	Ser	Ile	Arg	Arg	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly		
625					630					635					640		
Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Ser	Ala	Ser	Asn	Leu	Gln	Ser	Gly		
				645					650					655			
Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu		
			660					665					670				
Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln		
		675					680					685					
Gln	Ser	Tyr	Ile	Ile	Pro	Pro	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu		
	690						695					700					
Ile	Lys																
705																	
<210> SEQ ID NO 193																	
<211> LENGTH: 716																	
<212> TYPE: PRT																	
<213> ORGANISM: Artificial Sequence																	
<220> FEATURE:																	
<223> OTHER INFORMATION: Synthetic																	
<400> SEQUENCE: 193																	
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala		
1				5					10					15			
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Leu	Thr	Asp	Tyr		
			20					25					30				
Tyr	Met	Asn	Trp	Met	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
		35					40						45				
Gly	Val	Ile	Asn	Pro	Tyr	Asn	Gly	Asp	Thr	Ser	Tyr	Asn	Gln	Lys	Phe		
	50					55					60						
Lys	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr		
65					70					75					80		
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
				85					90					95			
Val	Arg	Asp	Asp	Gly	Tyr	Tyr	Val	His	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln		
			100					105						110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val		
		115					120					125					
Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala		
		130					135					140					

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Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	145	150	155	160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	165	170	175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	180	185	190	
Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	195	200	205	
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	210	215	220	
Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	225	230	235	240
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	245	250	255	
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	260	265	270	
Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	275	280	285	
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	290	295	300	
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	305	310	315	320
Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	325	330	335	
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	340	345	350	
Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	355	360	365	
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	370	375	380	
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	385	390	395	400
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	405	410	415	
Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	420	425	430	
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	435	440	445	
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val	Gln	Ser	450	455	460	
Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	465	470	475	480
Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	Tyr	Met	His	Trp	Val	Arg	Gln	485	490	495	
Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	Gly	Ile	Ile	Asn	Pro	Ser	Gly	500	505	510	
Gly	Arg	Thr	Ser	Tyr	Ala	Gln	Met	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	515	520	525	
Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	530	535	540	
Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Glu	Glu	Gln	545	550	555	560

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Trp	Pro	Val	Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	
			565						570					575		
Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	
			580					585					590			
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	
			595				600					605				
Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	
	610					615					620					
Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Arg	Arg	
625					630					635					640	
Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	
				645					650					655		
Ile	Tyr	Ser	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	
			660					665					670			
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	
		675					680					685				
Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ile	Ile	Pro	
	690					695					700					
Pro	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
705					710					715						
<210> SEQ ID NO 194																
<211> LENGTH: 214																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 194																
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	
1				5					10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Ser	Arg	
		20						25					30			
Leu	Thr	Trp	Leu	Gln	Gln	Lys	Pro	Glu	Lys	Ala	Pro	Lys	Arg	Leu	Ile	
		35					40					45				
Tyr	Ala	Thr	Ser	Ser	Leu	Asp	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
	50					55					60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
65					70					75					80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Tyr	Ala	Ser	Ser	Pro	Leu	
				85					90					95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	
			100						105					110		
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
		115					120					125				
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
						135					140					
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
145					150						155				160	
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
				165					170					175		
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	
			180					185					190			
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	
			195				200						205			

Phe Asn Arg Gly Glu Cys
210

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<210> SEQ ID NO 195
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 195

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Asp Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Glu
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

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<210> SEQ ID NO 196
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 196

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

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His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr
65					70					75					80
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
				85					90					95	
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			100					105					110		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
		115					120					125			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser
	130					135					140				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
145					150					155					160
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
				165					170					175	
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
			180					185					190		
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
	195						200					205			
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	210					215					220				
Pro	Gly	Lys													
225															
<210> SEQ ID NO 197															
<211> LENGTH: 225															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 197															
Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
1				5					10					15	
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
			20					25					30		
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
	35						40						45		
Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
	50					55					60				
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
65					70					75					80
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
				85					90					95	
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
			100					105					110		
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
	115						120						125		
Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
	130						135					140			
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
145					150					155					160
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
				165					170					175	
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
			180					185						190	

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Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
	195						200					205			
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
	210						215				220				
Lys															
225															
<210> SEQ ID NO 198															
<211> LENGTH: 232															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 198															
Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro
1				5					10					15	
Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
			20					25					30		
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
	35					40						45			
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val
	50					55				60					
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
65					70					75					80
Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln
				85					90					95	
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly
		100						105					110		
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro
	115						120					125			
Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr
	130					135					140				
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
145					150					155					160
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
			165						170					175	
Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
			180					185					190		
Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
	195						200					205			
Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
	210					215					220				
Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
225						230									
<210> SEQ ID NO 199															
<211> LENGTH: 226															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 199															
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
1				5					10					15	

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Gly	Pro	Asp	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			20					25					30			
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		35					40					45				
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
	50					55					60					
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	
65					70					75					80	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				85					90					95		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Glu	
			100					105					110			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		115					120					125				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	
	130					135					140					
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
145					150					155					160	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	
				165					170					175		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
			180					185					190			
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	
	195					200						205				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	
	210					215					220					
Pro	Gly															
225																
<210> SEQ ID NO 200																
<211> LENGTH: 226																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: Synthetic																
<400> SEQUENCE: 200																
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
1				5					10					15		
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	
			20					25					30			
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	
		35					40					45				
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
	50					55					60					
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	
65					70					75					80	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	
				85					90					95		
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
			100					105					110			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	
		115					120					125				
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	
	130					135					140					

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Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145          150          155          160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
          165          170          175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
          180          185          190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
          195          200          205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
          210          215          220

Pro Gly
225

<210> SEQ ID NO 201
<211> LENGTH: 224
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
1          5          10          15

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
          20          25          30

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
          35          40          45

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
          50          55          60

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
65          70          75          80

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
          85          90          95

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
          100          105          110

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
          115          120          125

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
          130          135          140

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
145          150          155          160

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
          165          170          175

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
          180          185          190

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
          195          200          205

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
          210          215          220

<210> SEQ ID NO 202
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 202																			
Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro				
1				5					10					15					
Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro				
			20					25						30					
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val				
		35					40					45							
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val				
	50					55				60									
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln				
65					70					75					80				
Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln				
				85					90					95					
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly				
		100						105					110						
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro				
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Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr				
	130					135					140								
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser				
145					150					155					160				
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			165						170					175					
Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr				
			180					185					190						
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		195					200					205							
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Tyr	Met	Asn	Trp	Met	Lys	Gln	Ser	His	Gly	Lys	Ser	Leu	Glu	Trp	Ile				
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Gly	Val	Ile	Asn	Pro	Tyr	Asn	Gly	Asp	Thr	Ser	Cys	Asn	Gln	Lys	Phe				
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Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr				
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Val	Arg	Asp	Asp	Gly	Tyr	Tyr	Val	His	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln				
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Gly	Thr	Thr	Leu	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
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Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
			180					185					190			
Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	
		195					200					205				
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	
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Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	
225					230					235					240	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
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Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	
			260					265					270			
Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
		275					280					285				
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
	290					295					300					
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Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	
				325					330					335		
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		340						345					350			
Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
		355					360					365				
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	370					375					380					
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Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	
			420					425					430			
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Leu	Thr	Trp	Leu	Gln	Gln	Glu	Pro	Asp	Gly	Thr	Ile	Lys	Arg	Leu	Ile
	35						40					45			
Tyr	Ala	Thr	Ser	Ser	Leu	Asp	Ser	Gly	Val	Pro	Lys	Arg	Phe	Asn	Gly
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Ser	Arg	Ser	Gly	Ser	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Ser
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Glu	Asp	Phe	Val	Asp	Tyr	Tyr	Cys	Leu	Gln	Tyr	Ala	Ser	Ser	Pro	Leu
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Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Thr	Val	Ala	Ala
			100					105					110		
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
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	130					135					140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150					155					160
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
		180						185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
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			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
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65					70					75					80
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
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Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
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Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
		115					120					125			
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
	130					135					140				
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
145					150					155					160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
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Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	
			180					185					190			
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	
		195					200					205				
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	210					215					220					
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	
225					230					235					240	
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	
			245						250					255		
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	
		260						265					270			
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	
	275						280					285				
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	
	290					295					300					
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	
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			20					25					30			
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
	35						40					45				
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
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Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	
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Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
			85						90					95		
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	
			100					105					110			
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	
		115					120					125				
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	
	130					135					140					
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	
145					150					155					160	
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	
			165						170					175		
Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	
			180					185					190			
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	
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Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	
210						215					220					
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	
225					230					235					240	
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	
			245						250					255		
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	
			260					265					270			
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	
		275					280					285				
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	
290						295					300					
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	
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Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys							
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			20					25					30			
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
		35					40					45				
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	50					55				60						
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
65					70					75					80	
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
			85						90					95		
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
			100					105					110			
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
		115					120					125				
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
		130				135					140					
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
145					150					155					160	
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
				165					170					175		
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
			180					185					190			
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
		195					200					205				
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
		210				215					220					
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
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Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
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Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
			260					265					270			
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
		275					280					285				
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	
	290					295					300					
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
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Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	
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Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
			85						90					95		
Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
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Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	
		115					120					125				
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	
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Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	
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Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	
			165						170					175		
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	
			180					185					190			
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	
	195						200					205				
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	
	210					215					220					
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	
225					230					235					240	
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	
			245						250					255		
Ser	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	
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Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	
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	290					295					300					
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	
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Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
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	50					55					60					
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	
65					70					75					80	
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
			85						90					95		
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	
			100					105					110			
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	
		115					120					125				
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	
						135					140					
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	
145					150					155					160	
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	
			165						170					175		
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	
			180					185					190			
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	
		195					200					205				
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	
	210					215					220					
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	
225					230					235					240	
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	
			245						250					255		
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	
			260					265					270			
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	
		275					280					285				
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	
	290						295					300				

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

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<210> SEQ ID NO 211
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 211

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly
325

<210> SEQ ID NO 212
<211> LENGTH: 325
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 212

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly
325

<210> SEQ ID NO 213
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 213

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
325 330

<210> SEQ ID NO 214
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 214

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55				60					
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70				75					80	
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
			100					105					110		
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
		115					120					125			
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
	130					135					140				
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
145					150					155					160
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
			165						170					175	
Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
			180					185					190		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
		195					200					205			
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
	210					215					220				
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
225					230					235					240
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
			245						250					255	
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
			260					265					270		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
		275					280					285			
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
	290					295					300				
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
305					310					315					320
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Ala						
			325						330						
<210> SEQ ID NO 215															
<211> LENGTH: 327															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 215															
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
1				5					10					15	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
		20						25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			

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Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
50						55				60						
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
65					70				75					80		
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
			85						90					95		
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	
			100					105					110			
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
		115					120					125				
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
		130				135					140					
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
145					150					155					160	
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
				165					170					175		
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
			180					185					190			
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
		195					200					205				
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
		210				215					220					
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
225					230					235				240		
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
				245					250					255		
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
		260						265					270			
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
		275					280					285				
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	
		290				295					300					
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
305					310				315						320	
Leu	Ser	Leu	Ser	Leu	Gly	Ala										
				325												

<210> SEQ ID NO 216
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 216

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr
20 25 30

<210> SEQ ID NO 217
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

Asp Arg Val Thr Ile Pro Cys
20

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<210> SEQ ID NO 228
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 228

Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 229
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 229

Phe Gly Glu Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> SEQ ID NO 230
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 230

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr
20 25 30

<210> SEQ ID NO 231
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 231

Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met Gly
1 5 10

<210> SEQ ID NO 232
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 232

Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Thr
20 25 30

<210> SEQ ID NO 233
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 233

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<210> SEQ ID NO 239
<211> LENGTH: 30
<212> TYPE: PRT
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<210> SEQ ID NO 244
<211> LENGTH: 32
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<400> SEQUENCE: 244

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Gly Ile Tyr Tyr Cys
20 25 30

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<210> SEQ ID NO 245
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 245

Phe Gly Gly Gly Thr Lys Leu Glu Phe Lys
1 5 10

```
<210> SEQ ID NO 246
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 246

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

```
<210> SEQ ID NO 247
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 247

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

```
<210> SEQ ID NO 248
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 248

Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
1 5 10 15

Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

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<210> SEQ ID NO 249
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 249

Gln Pro Ala Ser Ile Ser Cys
20

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<210> SEQ ID NO 250
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 250

Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Arg Val Leu Ile Tyr
1 5 10 15

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<210> SEQ ID NO 251
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 251

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
20 25 30

```
<210> SEQ ID NO 252
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 252

Phe Gly Arg Gly Thr Lys Leu Glu Ile Lys
1 5 10

```
<210> SEQ ID NO 253
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
```

<400> SEQUENCE: 253

Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser
20 25 30

```
<210> SEQ ID NO 254
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 254

Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Ala
1 5 10

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<210> SEQ ID NO 255
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 255

Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val Val Leu Thr
1 5 10 15

Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
20 25 30

<210> SEQ ID NO 256
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 256

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys
20

<210> SEQ ID NO 257
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 257

Trp Val Gln Gln Lys Pro Gly Gln Leu Phe Arg Gly Leu Ile Gly
1 5 10 15

<210> SEQ ID NO 258
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 258

Trp Val Pro Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala
1 5 10 15

Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Phe Cys
20 25 30

<210> SEQ ID NO 259
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 259

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
1 5 10

<210> SEQ ID NO 260
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 260

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> SEQ ID NO 261
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 261

Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> SEQ ID NO 262
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 262

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> SEQ ID NO 263
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 263

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
20 25 30

<210> SEQ ID NO 264
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 264

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
1 5 10

<210> SEQ ID NO 265
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 265
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
20 25 30

<210> SEQ ID NO 266
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 266
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 267
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 267
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys
20

<210> SEQ ID NO 268
<211> LENGTH: 15
<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 268
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 269
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 269
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 270
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 270
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1 5 10

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<210> SEQ ID NO 271
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 271

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Tyr Thr Phe Thr
 20 25 30

<210> SEQ ID NO 272
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 272

Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> SEQ ID NO 273
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 273

Arg Thr Thr Ser Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Arg Leu Arg Ser Asp Asp Thr Val Val Tyr Tyr Cys Thr Arg
 20 25 30

<210> SEQ ID NO 274
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 274

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 275
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 275

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Phe Thr Cys
 20

<210> SEQ ID NO 276
<211> LENGTH: 10
<212> TYPE: PRT

Phe Gly Ala Gly Thr Lys Leu Asp Leu Lys
1 5 10

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<210> SEQ ID NO 282
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 282

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> SEQ ID NO 283
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 283

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
 20 25 30

<210> SEQ ID NO 284
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 284

Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 20 25 30

<210> SEQ ID NO 285
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 285

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys
 20

<210> SEQ ID NO 286
<211> LENGTH: 15
<212> TYPE: PRT
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 286

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 287
<211> LENGTH: 32
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 287

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Asn Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 288
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 288

Arg Val Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
20 25 30

<210> SEQ ID NO 289
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 289

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> SEQ ID NO 290
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 290

Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 291
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 291

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 292
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic														
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Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
1				5					10					
<210> SEQ ID NO 293														
<211> LENGTH: 14														
<212> TYPE: PRT														
<213> ORGANISM: Artificial Sequence														
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<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 293														
Trp	Met	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	Gly	
1				5					10					
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<212> TYPE: PRT														
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<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 294														
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val Gly
1				5					10					15
Asp Arg Val Thr Ile Ser Cys														
20														
<210> SEQ ID NO 295														
<211> LENGTH: 15														
<212> TYPE: PRT														
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<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 295														
Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Lys
1				5					10					15
<210> SEQ ID NO 296														
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<212> TYPE: PRT														
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<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 296														
Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe Thr
1				5					10					15
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys														
20 25 30														
<210> SEQ ID NO 297														
<211> LENGTH: 32														
<212> TYPE: PRT														
<213> ORGANISM: Artificial Sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: Synthetic														
<400> SEQUENCE: 297														
Lys	Ala	Thr	Met	Thr	Arg	Asp	Lys	Ser	Ser	Ser	Thr	Val	Tyr	Met Glu
1				5					10					15

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Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
			20					25					30		
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<211> LENGTH: 32															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 298															
Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys
			20					25					30		
<210> SEQ ID NO 299															
<211> LENGTH: 10															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 299															
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys						
1				5					10						
<210> SEQ ID NO 300															
<211> LENGTH: 32															
<212> TYPE: PRT															
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<220> FEATURE:															
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<400> SEQUENCE: 300															
Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr	Met	Glu
1				5					10					15	
Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
			20					25					30		
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<211> LENGTH: 32															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 301															
Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	Met	Glu
1				5					10					15	
Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
			20					25					30		
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<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic															
<400> SEQUENCE: 302															
Asp	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
1				5					10					15	

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Ser	Leu	Ser	Leu	Thr	Cys	Thr	Val	Thr	Gly	Tyr	Ser	Ile	Thr
			20					25					30
<210> SEQ ID NO 303													
<211> LENGTH: 14													
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<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 303													
Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Lys	Leu	Glu	Trp	Met	Gly
1				5					10				
<210> SEQ ID NO 304													
<211> LENGTH: 32													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 304													
Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
1				5					10				15
Leu	Asn	Ser	Val	Thr	Thr	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
			20					25					30
<210> SEQ ID NO 305													
<211> LENGTH: 23													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 305													
Asp	Ile	Val	Met	Thr	Gln	Ser	His	Lys	Phe	Met	Ser	Thr	Ser
1				5					10				15
Asp	Arg	Val	Ser	Ile	Thr	Cys							
				20									
<210> SEQ ID NO 306													
<211> LENGTH: 15													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 306													
Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Leu	Leu	Ile
1				5					10				15
<210> SEQ ID NO 307													
<211> LENGTH: 32													
<212> TYPE: PRT													
<213> ORGANISM: Artificial Sequence													
<220> FEATURE:													
<223> OTHER INFORMATION: Synthetic													
<400> SEQUENCE: 307													
Gly	Val	Pro	Asp	Arg	Phe	Thr	Gly	Ser	Gly	Ser	Gly	Thr	Asp
1				5					10				15
Leu	Thr	Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Leu	Ala	Leu	Tyr
				20				25				30	

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<210> SEQ ID NO 313
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 313

Glu Ile Val Leu Thr Gln Ser Pro Val Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys
20

<210> SEQ ID NO 314

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<211> LENGTH: 15
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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 314

Trp Tyr Leu Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Lys
1 5 10 15

<210> SEQ ID NO 315

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<211> LENGTH: 31
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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 315

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu
1 5 10 15

Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 316

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<211> LENGTH: 30
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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 316

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr
20 25 30

<210> SEQ ID NO 317

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 317

Trp Met Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> SEQ ID NO 318

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<211> LENGTH: 32
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<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 318
Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15
Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
20 25 30

<210> SEQ ID NO 319
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<400> SEQUENCE: 319
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 320
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 320
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys
20

<210> SEQ ID NO 321
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 321
Trp Leu Gln Gln Lys Pro Glu Lys Ala Pro Lys Arg Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 322
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 322
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 323
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 323
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1 5 10

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<210> SEQ ID NO 324
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 324

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
 20 25 30

<210> SEQ ID NO 325
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 325

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1 5 10

<210> SEQ ID NO 326
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 326

Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 20 25 30

<210> SEQ ID NO 327
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 327

Trp Leu Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 328
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 328

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Ser
 20 25 30

<210> SEQ ID NO 329
<211> LENGTH: 15
<212> TYPE: PRT

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<210> SEQ ID NO 334
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 334																			
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly				
1				5					10					15					
Asp	Arg	Val	Thr	Ile	Thr	Cys													
				20															
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<211> LENGTH: 18																			
<212> TYPE: PRT																			
<213> ORGANISM: Artificial Sequence																			
<220> FEATURE:																			
<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 335																			
Trp	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu				
1				5					10					15					
Ile	Tyr																		
<210> SEQ ID NO 336																			
<211> LENGTH: 32																			
<212> TYPE: PRT																			
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<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 336																			
Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr				
1				5					10					15					
Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys				
				20				25					30						
<210> SEQ ID NO 337																			
<211> LENGTH: 10																			
<212> TYPE: PRT																			
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<223> OTHER INFORMATION: Synthetic																			
<400> SEQUENCE: 337																			
Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys										
1				5					10										

- What is claimed is:
1. A bispecific antagonist, comprising a first targeting domain and a second targeting domain:
wherein the first targeting domain binds specifically to human LAG-3 and comprises:
(1) an immunoglobulin HCVR comprising three HCDRs: HCDR1, HCDR2 and HCDR3,
wherein the HCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 163, 166 and 169,
wherein the HCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 164, 167 and 170, and
wherein the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 165, 168 and 171; and
(2) an immunoglobulin LCVR comprising three LCDRs: LCDR1, LCDR2 and LCDR3,
wherein the LCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 172, 175 and 177,

wherein the LCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 173 and 178, and
wherein the LCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 174, 176 and 179.

2. The bispecific antagonist of claim 1, wherein the second targeting domain binds specifically to human TIGIT.

3. The bispecific antagonist of claim 2, wherein the second targeting domain comprises:
(I) an immunoglobulin HCVR comprising three HCDRs: HCDR1, HCDR2 and HCDR3,
wherein the HCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 6, 11, 15, 17, 20 and 23,
wherein the HCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 7, 9, 12, 13, 16, 18, 21 and 24, and
wherein the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 5, 8, 10, 14, 19, 22 and 25; and

263

(2) an immunoglobulin LCVR comprising three LCDRs: LCDR1, LCDR2 and LCDR3, wherein the LCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 26, 29, 31, 33, 35, 39, 42 and 45, wherein the LCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 27, 30, 36, 37, 40, 43 and 46, and wherein the LCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 34, 38, 41, 44 and 47.

4. The bispecific antagonist of claim 3, wherein the second targeting domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:23, an HCDR2 comprising the amino acid sequence of SEQ ID NO:24, an HCDR3 comprising the amino acid sequence of SEQ ID NO:25, an LCDR1 comprising the amino acid sequence of SEQ ID NO:45, an LCDR2 comprising the amino acid sequence of SEQ ID NO:46, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:47.

5. The bispecific antagonist of claim 4, wherein the second targeting domain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:67.

6. The bispecific antagonist of claim 1, wherein the second targeting domain binds specifically to human PD-1.

7. The bispecific antagonist of claim 6, wherein the second targeting domain comprises:

(1) an immunoglobulin HCVR comprising three complementarity determining regions (HCDRs): HCDR1, HCDR2 and HCDR3,

wherein the HCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:68, 71, 74, 76 and 79,

wherein the HCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:69, 72, 77 and 80, and

wherein the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:70, 73, 75, 78 and 81; and

(2) an immunoglobulin LCVR comprising three complementarity determining regions (LCDRs): LCDR1, LCDR2 and LCDR3,

wherein the LCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:82, 85, 88, 89, 90 and 93,

wherein the LCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:83, 86, 91 and 94, and

wherein the LCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:84, 87, 92 and 95.

8. The bispecific antagonist of claim 7, wherein the second targeting domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:76, an HCDR2 comprising the amino acid sequence of SEQ ID NO:77, an HCDR3 comprising the amino acid sequence of SEQ ID NO:78, a LCDR1 comprising the amino acid sequence of SEQ ID NO:90, a LCDR2 comprising the amino acid sequence of SEQ ID NO:91, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:92.

9. The bispecific antagonist of claim 8, wherein the second targeting domain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:104 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:105.

264

10. The bispecific antagonist of claim 7, wherein the second targeting domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:79, an HCDR2 comprising the amino acid sequence of SEQ ID NO:80, an HCDR3 comprising the amino acid sequence of SEQ ID NO:81, a LCDR1 comprising the amino acid sequence of SEQ ID NO:93, a LCDR2 comprising the amino acid sequence of SEQ ID NO:94, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:95.

11. The bispecific antagonist of claim 10, wherein the second targeting domain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:107.

12. The bispecific antagonist of claim 1, wherein the second targeting domain binds specifically to human PD-L1.

13. The bispecific antagonist of claim 12, wherein the second targeting domain comprises:

(1) an immunoglobulin HCVR comprising three complementarity determining regions (HCDRs): HCDR1, HCDR2 and HCDR3,

wherein the HCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 108, 111, 117 and 120,

wherein the HCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 109, 112, 114, 116, 118, 121 and 125, and

wherein the HCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 110, 113, 115, 119 and 122; and

(2) an immunoglobulin LCVR comprising three LCDRs: LCDR1, LCDR2 and LCDR3,

wherein the LCDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 123, 126, 130, 133 and 136,

wherein the LCDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 126, 127, 131, 134 and 137, and

wherein the LCDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 125, 128, 129, 132, 135 and 138.

14. The bispecific antagonist of claim 13, wherein the second targeting domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO:111, an HCDR2 comprising the amino acid sequence of SEQ ID NO:114, an HCDR3 comprising the amino acid sequence of SEQ ID NO:115, a LCDR1 comprising the amino acid sequence of SEQ ID NO:123, a LCDR2 comprising the amino acid sequence of SEQ ID NO:124, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:125.

15. The bispecific antagonist of claim 14, wherein the second targeting domain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:153 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:154.

16. A method of treating a cell proliferative disorder in a subject, comprising:

administering to a subject in need thereof an effective amount of the antagonist of claim 1.

17. A method of treating a cell proliferative disorder in a subject, comprising:

administering to a subject in need thereof an effective amount of the antagonist of claim 1.

18. A method of treating a cell proliferative disorder in a subject, comprising:

administering to a subject in need thereof an effective amount of the antagonist of claim 6.

265

266

19. A method of treating a cell proliferative disorder in a subject, comprising:
administering to a subject in need thereof an effective amount of the antagonist of claim **12**.

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